Journal of Rheumatology Research
JRR, 2(1): 84-86
www.scitcentral.com

ISSN: 2641-6999

Case Report: Open Access

# Anti-Dense Fine Speckled Autoantibodies (DFS70) Titers Decrease in Successful Treatment of Uveitis Associated with Juvenile Idiopathic Arthritis

**Schmeling H[1*], Chomistek KM[1], Choi MY[2] and Fritzler MJ[2]**

*[*1]Section of Rheumatology, Department of Pediatrics, Cumming School of Medicine, University of Calgary, Alberta Children's Hospital, Canada*

*[2]Department of Medicine, Cumming School of Medicine, University of Calgary, Canada.*

*Received October 10, 2019; Accepted October 22, 2019; Published December 09, 2019*

## ABSTRACT

Uveitis is the most common extra-articular manifestation of Juvenile Idiopathic Arthritis (JIA). It is commonly asymptomatic and, if unrecognized and untreated, can lead to blindness. The identification of new diagnostic and/or predictive biomarkers would improve the identification of children who are at high risk for uveitis and also to monitor disease activity. Autoantibodies directed to the Dense Fine Speckled antigen (DFS70), also known as Lens Epithelium-Derived Growth Factor (LEDGF), have been described in a number of conditions including eye-related pathologies such as Vogt-Koyanagi-Harada syndrome. We present two cases of oligoarticular JIA-associated uveitis (JIA-U) with high titer antinuclear antibodies (ANA) that were identified as DFS70 autoantibodies at the time of active bilateral uveitis. Anti-DFS70 titres normalized following treatment of uveitis with methotrexate and/or etanercept while ANA targeting other intracellular antigens remained positive. This report suggests that anti-DFS70 autoantibodies may be a potential risk factor and useful indicator of disease activity for JIA-U. Additional multi-center and longitudinal studies would be important to validate these findings.

## BACKGROUND

Juvenile Idiopathic Arthritis (JIA) is complicated by a high frequency of uveitis (JIA-U) marked by inflammation of the anterior uveal tract [1]. The prediction and detection of uveitis is a diagnostic challenge because it is often asymptomatic and if untreated can lead to blindness [1,2]. Antinuclear Antibodies (ANA), observed in 65-66% of JIA-U, have been regarded as a biomarker associated with uveitis but has limited specificity because a positive conventional ANA test is also seen in 37-47% of JIA without uveitis [1]. Autoantibodies producing a Dense Fine Speckled (DFS) immunofluorescence pattern often react with the 70 kDa DFS70 antigen (also known as lens epithelium-derived growth factor) [3,4]. Anti-DFS70 was reported in a variety of conditions such as atopic dermatitis, eye diseases, juvenile localized scleroderma, juvenile idiopathic arthritis, juvenile localized scleroderma, juvenile dermatomyositis and prostate cancer [3,5] and was shown to be of higher frequency in young females [4,6]. Although some evidence indicates that anti-DFS70 antibodies are stable over time [4], little is known if anti-DFS70 titers are influenced by disease activity or certain therapeutic interventions. This consideration might have important clinical implications providing clinicians with an additional sensitive parameter of disease activity and facilitate evidence-based treatment decisions.

We report two patients with ANA positive oligoarticular JIA-U who tested highly positive for anti-DFS70 antibodies by a Chemiluminescence Immunoassay (CIA) at the time of active uveitis. However, the test became negative after the uveitis was in remission.

## CASE REPORT

The first patient was a healthy male who was diagnosed at one year of age with an ANA positive, persistent oligoarticular JIA. Recurrent flares of knee arthritis were treated with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), Intraarticular Glucocorticoids (IAS) and Methotrexate (MTX). At eight years of age, he was diagnosed with a chronic relapsing bilateral uveitis which was not controlled with prednisolone eye drops and MTX. At the time of active uveitis, the ANA was positive at a titer of 1:1280 with a DFS Indirect Immunofluorescence (IIF) pattern International Consensus on ANA Patterns (ICAP),

**Corresponding author:** Heinrike Schmeling, MD, Assistant Professor, Section of Rheumatology, Department of Pediatrics, Cumming School of Medicine, University of Calgary, Alberta Children's Hospital, Canada, Tel: +1 403 955 7771; Fax: +1-403 955 7649; E-mail: heinrike.schmeling@albertahealthservices.ca

**Citation:** Schmeling H, Chomistek KM, Choi MY & Fritzler MJ. (2019) Anti-Dense Fine Speckled Autoantibodies (DFS70) Titers Decrease in Successful Treatment of Uveitis Associated with Juvenile Idiopathic Arthritis. J Rheumatol Res, 2(1): 84-86.

AC-2, http://www.anapatterns.org/ on HEp2 cells (Immuno Concepts Inc., Sacramento), consistent with anti-DFS70 reactivity [5]. Anti-DFS70 autoantibody reactivity was confirmed by CIA (38.2 chemiluminescence units [CU]: normal range <20 CU) (CIA: Inova Diagnostics Inc., San Diego, CA, USA). The uveitis was successfully treated with a combination of MTX, Etanercept and topical prednisolone eye drops. At 11 years of age when both his arthritis and uveitis were in remission, his anti-DFS70 CIA test was negative (CU<5). Although ANA titers had markedly decreased, they remained positive at a titer of 1:160. Further testing using autoantibody arrays (Connective 13, TheraDiag, Paris, France) failed to disclose the remaining autoantibody.

The second case was a previously healthy girl diagnosed at five years of age with an ANA positive oligoarticular JIA, treated with NSAIDs and IAS. One year later, she developed a flare of arthritis and asymptomatic bilateral uveitis. The ANA was positive at a titer of 1:5120 with a DFS IIF pattern (AC-2) and the anti-DFS70 CIA test was highly positive (131.5 CU). The arthritis remained in remission after treatment with NSAIDs and IAS, but the uveitis was not controlled with topical therapy, therefore MTX was started. Approximately one year later when her arthritis and uveitis were in remission, the anti-DFS70 CIA was below the normal cut-off (CU<5), although the ANA remained positive at a titer of 1:5120 with a homogenous and speckled nuclear pattern (AC-1; AC-3). Further testing using autoantibody arrays (Connective 13, TheraDiag, Paris, France) found antibodies to histones as one of the remaining autoantibodies.

## DISCUSSION

A previous study reported anti-DFS70 as detected by CIA in 2.1% of healthy children and in 4.5% of pediatric sera referred for ANA testing [5]. In this study of small disease cohorts, the frequency of anti-DFS70 was highest in juvenile dermatomyositis (18.2%) and juvenile localized scleroderma (13.8%), but less common in childhood systemic lupus erythematosus (5.7%), diffuse cutaneous systemic sclerosis (4.5%), celiac disease (4.1%) and JIA (2.5%). Of note, anti-DFS70 antibodies were observed 11.5% of children with uveitis and JIA-U. However, there have been no reported studies of pediatric disease cohorts to determine the sustainability of the anti-DFS70 response over time.

DFS70 is a chromatin-associated protein that protects cells from stress-induced apoptosis including heat shock, oxidative stress, UV damage and serum starvation [3,7-9]. Of interest, anti-DFS70 has been shown to be toxic to lens epithelial cells, keratinocytes and fibroblasts [9]. The importance of these findings is supported by several reports that have found an association between anti-DFS70 and eye-related pathologies [10,11]. For example, a report indicated that sera from chronic uveitis patients with Vogt-Koyangi-Harada disease had a significantly higher prevalence of anti-DFS70 antibodies compared to healthy controls (24/36 vs. 8/37, $p<0.001$) [10]. Interestingly, in patients with Behçets disease and sarcoidosis associated panuveitis, the prevalence of anti-DFS70 antibodies (34% and 25%) was almost same as apparently healthy controls (22%), suggesting that the autoimmunity against DFS70 is not a secondary phenomenon caused by a B cell response to tissue damage [10]. Another group detected autoantibodies to DFS70 using ELISA in 71.4% of 21 Japanese atopic dermatitis patients and 8/8 of the patients who also had cataracts tested positive and cytotoxic activity of the anti-DFS70 against lens epithelial cells was reported [11]. It was suggested that binding of the autoantibodies to released DFS70 autoantigen has a pathogenic role by preventing its uptake by local tissue cells [11], whereas anti-DFS70 autoantibodies may be protective [12]. Last, although the hormonal status of pre-pubertal females is likely not a factor, a more recent report indicated that the hormonal status of adult females may influence anti-DFS70 titres [13].

Nevertheless, the pathogenic role of DFS70 autoantibodies in various eye related inflammatory conditions remains unclear. It is uncertain whether this autoimmunity is the primary cause of disease or a secondary phenomenon by triggering the elicitation of DFS70 autoantibodies in a pro-inflammatory context. In the latter case, control of inflammation such as in our cases might then lead to a decreased titer or disappearance of DFS70 autoantibodies. Accordingly, based on our case reports, anti-DFS70 antibodies may serve as an indicator for successful therapy and remission of uveitis in JIA. Further systematic investigations are required to determine if certain therapeutics (i.e., MTX, Etanercept) influence anti-DFS70 titers. In our patients, anti-DFS70 antibodies became negative in one patient following treatment with MTX, and in the other after starting Etanercept in combination with MTX.

In our case reports, we noted that the IIF ANA remained positive despite a decrease of anti-DFS70 to within normal range as detected by CIA. This observation cannot be readily explained by autoantibody isotype differences because both the ANA and CIA use anti-human IgG secondary antibodies. Neither can it be explained by decreased sensitivity of CIA because earlier studies have shown that CIA is both highly sensitive and specific for anti-DFS70 [14]. A plausible explanation is that a second autoantibody such as a molecular ligand or 'partner' of DFS70, such as methyl CpG binding protein 2 (MeCP2) [15], may be unaffected by therapeutic intervention. Indeed, earlier studies in our lab have shown that some anti-DFS70 sera when assayed by western immunoblot show reactivity to a second protein of similar molecular mass (unpublished). In a recent published study of sera that had the DFS70-IIF pattern, autoantibodies directed to MeCP2, a molecular 'partner' of DFS70, were not detected [11]. However, since this study did not focus on

anti-MeCP2 in specific conditions, it would be important to test uveitis sera for this reactivity.

If these observations are validated, the identification of the anti-DFS70 autoantibody as an additional biomarker and risk factor for the development of JIA-U will allow an earlier diagnosis and expedite the initiation of treatment with the goal to prevent morbidity such as vision loss and/or blindness. In addition, if anti-DFS70 continue to be positive during the disease course it might indicate a higher risk for uveitis flares and might therefore, determine and guide frequency of ophthalmologic examination and screening. Furthermore, this is the first report of anti-DFS70 autoantibodies becoming negative after treatment and/or disease remission which implies a pathogenic role of the autoantibodies as well as serving as a useful indicator for disease activity. Accordingly, the clinical use of anti-DFS has the potential to greatly impact patient care and clinical outcomes in children with JIA-U.

## CONCLUSION

Anti-DFS70 is a potential risk factor and changes in titers may be an indicator of disease activity for JIA-associated uveitis.

## ACKNOWLEDGMENT

The authors wish to thank the patients and their family for allowing this paper to be published and Haiyan Hou and Meifeng Zhang (Mitogen Advanced Diagnostics, Calgary, AB Canada) for laboratory analyses.

## CONSENT

Written consent from patients and/or their legal guardians was obtained. In addition, this case review was carried out in compliance with the Helsinki Declaration of 1975 for human studies as revised in 2013.

## CONFLICT OF INTEREST

Three authors (HS, KC, MYC) have no conflicts of interests. MJF is a paid consultant, has received honoraria or has received gifts in kind from Inova Diagnostics (San Diego, CA).

## REFERENCES

1. Heiligenhaus A, Heinz C, Edelsten C, Kotaniemi K, Minden K (2013) Review for disease of the year: Epidemiology of juvenile idiopathic arthritis and its associated uveitis: The probable risk factors. Ocul Immunol Inflamm 21: 180-191.
2. Prakken B, Albani S, Martini A (2011) Juvenile idiopathic arthritis. Lancet 377: 2138-2149.
3. Ochs RL, Mahler M, Basu A, Rios-Colon L, Sanchez TW, et al. (2016) The significance of autoantibodies to DFS70/LEDGFp75 in health and disease: Integrating basic science with clinical understanding. Clin Exp Med 16: 273-293.
4. Mahler M, Andrade LE, Casiano CA, Malyavantham K, Fritzler MJ (2019) Anti-DFS70 antibodies: An update on our current understanding and their clinical usefulness. Expert Rev Clin Immunol 15: 241-250.
5. Schmeling H, Mahler M, Levy DM, Moore K, Stevens AM, et al. (2015) Autoantibodies to dense fine speckles in pediatric diseases and controls. J Rheumatol 42: 2419-2426.
6. Raissi TC, Hewson C, Pope JE (2018) Repeat testing of antibodies and complements in systemic lupus erythematosus: When is it enough? J Rheumatol 45: 827-834.
7. Ganapathy V, Casiano CA (2004) Autoimmunity to the nuclear autoantigen DFS70 (LEDGF): What exactly are the autoantibodies trying to tell us? Arthritis Rheum 50: 684-688.
8. Mahler M, Hanly JG, Fritzler MJ (2012) Importance of the dense fine speckled pattern on HEp-2 cells and anti-DFS70 antibodies for the diagnosis of systemic autoimmune diseases. Autoimmun Rev 11: 642-645.
9. Singh DP, Ohguro N, Kikuchi T, Sueno T, Reddy VN, et al. (2000) Lens epithelium-derived growth factor: Effects on growth and survival of lens epithelial cells, keratinocytes and fibroblasts. Biochem Biophys Res Commun 267: 373-381.
10. Yamada K, Senju S, Shinohara T, Nakatsura T, Murata Y, et al. (2001) Humoral immune response directed against LEDGF in patients with VKH. Immunol Lett 78: 161-168.
11. Ayaki M, Ohoguro N, Azuma N, Majima Y, Yata K, et al. (2002) Detection of cytotoxic anti-LEDGF autoantibodies in atopic dermatitis. Autoimmunity 35: 319-327.
12. Infantino M, Carbone T, Manfredi M, Grossi V, Benucci M, et al. (2019) Are anti-DFS70 autoantibodies protective? Isr Med Assoc J 21: 509-511.
13. Miyachi K, Ihara A, Ihara M, Yamamoto K, Sasse B, et al. (2019) Anti-DFS70 autoantibodies in Japanese women at different menstrual stages. J Rheumatol Res 1: 24-32.
14. Mahler M, Parker T, Peebles CL, Andrade LE, Swart A, et al. (2012) Anti-DFS70/LEDGF antibodies are more prevalent in healthy individuals compared to patients with systemic autoimmune rheumatic diseases. J Rheumatol 39: 2104-2110.
15. Basu A, Woods-Burnham L, Ortiz G, Rios-Colon L, Figueroa J, et al. (2015) Specificity of antinuclear autoantibodies recognizing the dense fine speckled nuclear pattern: Preferential targeting of DFS70/LEDGFp75 over its interacting partner MeCP2. Clin Immunol 16: 241-250.