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OP0034

A NOVEL SERUM CALPROTECTIN (MRP8/14) PARTICLE ENHANCED IMMUNO-TURBIDIMETRIC ASSAY (SCAL TURBO) HELPS TO DIFFERENTIATE SJIA FROM OTHER DISEASES IN ROUTINE CLINICAL LABORATORY SETTINGS

Keywords: Innate immunity, Diagnostic Tests, Biomarkers

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Background: Differential diagnosis in children with signs of unprovoked inflammation can be challenging. In particular, differentiating systemic-onset juvenile idiopathic arthritis (SJIA) from other diagnoses is difficult in individuals presenting with fever of unknown origin. We have recently validated myeloid-related protein 8/14 (MRP8/14, S100A8/A9, calprotectin) serum analyses as a helpful tool supporting the diagnosis of SJIA. The results could be confirmed with a commercial ELISA. However, further optimization of the analytical technology will be important to enable large-scale use in routine laboratory settings.
Objectives: To evaluate the accuracy in identifying children with SJIA, the performance of an immunoturbidimetric assay for measurements of serum-calprotectin (BÜHLMANN sCAL turbo) on an automated laboratory instrument was tested in serum samples of children with various conditions.
Methods: Samples from 650 children were available with diagnoses SJIA (n=99), non-systemic JIA (n=169), infections (n=51), other inflammatory diseases (n=161), and acute lymphatic leukemia (ALL, n=147). In addition, samples from 23 healthy controls were included. The patients with systemic inflammatory diseases were collected at Muenster University as reported before.[1] Patients with non-systemic JIA were from the Nordic JIA cohort as previously described in detail.[2] The ALL cohort included consecutive cases from Aalborg and Aarhus University Hospitals.[3] The BÜHLMANN sCAL turbo test is a particle enhanced immuno-turbidimetric assay (PETIA) and was compared to the established MRP8/14 ELISA from BÜHLMANN (EK-MRP8/14). The sCAL PETIA has a range of 230-15,000 ng/mL (extended range up to 225,000 ng/ml by dilution of 1:15) in sample volumes of only 2-3 µl and was implemented into the automated laboratory setting at the central clinical laboratory of the University Hospital Muenster as a rapid test available on demand.
Results: The sCAL turbo assay showed an excellent correlation to the MRP8/14 ELISA used in the previous validation studies (r=0.99, p<0.001). It could reliably differentiate SJIA from all other diagnoses with significant accuracy (cut-off at 9,100 ng/ml, sensitivity 93%, specificity 87%, ROC area under curve 0.961, p<0.001). Results are shown in Table 1 and Figure 1.

Table 1. Accuracy (ROC analyses) of sCAL turbo measurements in differentiating groups of patients

	SJIA vs all groups	*SJIA vs infections*	*SJIA vs ALL*	*SJIA vs others*
AUC (95%CI)	0.961 (0.943-0.978)	0.908 (0.862-0.953)	0.992 (0.985-0.999)	0.958 (0.934-0.981)
Cut-Off (ng/ml)	9,100	10,500	9,100	9,100
Sensitivity (%)	93	82	99	93
Specificity (%)	87	84	87	86

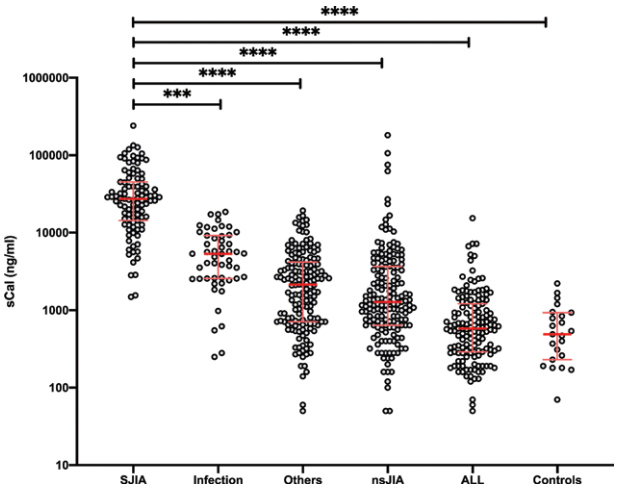

Figure 1. Results of sCAL turbo measurements in different groups of patients (red line showing median, error bars showing interquartile range; *** p<0.001, **** p<0.0001)

Conclusion: MRP8/14 (S100A8/A9, calprotectin) serum analyses have been validated as a helpful tool supporting the diagnosis of SJIA in children with prolonged fever or inflammatory disease. Here we show that an immunoturbidimetric assay for detection of serum-calprotectin on an automated laboratory instrument can be implemented in clinical laboratory settings to facilitate its use as a diagnostic routine test in clinical practice.

REFERENCES:

[1] Park C, Miranda-Garcia M, Berendes R, et al. MRP8/14 serum levels as diagnostic markers for systemic juvenile idiopathic arthritis in children with prolonged fever. *Rheumatol*. 2022;61(7):3082-3092.
[2] Glerup M, Rypdal V, Herlin T et al. Long-Term Outcomes in Juvenile Idiopathic Arthritis: Eighteen Years of Follow-Up in the Population-Based Nordic Juvenile Idiopathic Arthritis Cohort. *Arthritis Care Res*. 2019;72(4):507-516.
[3] Brix N, Kessel C, Foell D et al. Phagocyte-related S100 proteins and cytokines in Acute Lymphoblastic Leukemia at diagnosis and follow-up and their prognostic value may improve prediction of minimal residual disease. *Leuk Lymphoma* 2022 (in print)

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OP0035

THE USE OF CHILDHOOD LLDAS: FIRST RESULTS IN A REAL-LIFE LONGITUDINAL CHILDHOOD LUPUS COHORT SHOW GOOD FEASIBILITY BUT DIFFICULT ATTAINMENT

Keywords: Treat to target, Systemic lupus erythematosus

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Background: Almost half of childhood-onset SLE (cSLE) patients show damage within 5 years after disease onset, which is partially disease- and partially

drug-related [1]. Therefore, the challenge in (c)SLE is not only to lower disease activity, but also to minimalize glucocorticoid toxicity. Treat-to-target (T2T) has been a new type of approach to improve long-term patient outcomes by adapting treatment regimens until the target is met. For T2T, the concept of Lupus-Low-Disease-Activity-State (LLDAS) as a target in SLE has been defined which contains a SLE disease activity index (SLEDAI) ≤ 4 and a maximum prednisolone use of 7.5mg/day [2]. This adult LLDAS (aLLDAS) has been shown to be a feasible target in cSLE patients and attainment leads to lowering risk for severe flare and cumulative damage [3]. Another cSLE cohort study demonstrated that all patients were able to reach aLLDAS (median 186 days) and 72.5% remained in aLLDAS >50% of time [4]. Recently, an international cSLE T2T Task Force has adapted the LLDAS definition specifically for cSLE patients (cLLDAS) by Delphi surveys and consensus meetings, with an addition of a calculated prednisolone dose per body weight in maximum dose of 0.15 mg/kg/day and an absolute maximum of 7,5 mg/day (Smith et al., submitted).

Objectives: The first objective was to investigate if the time to reach first aLLDAS and cLLDAS differs in cSLE. The second objective was to observe if cSLE patients maintain in cLLDAS for 50% of follow-up time (cLLDAS-50).

Methods: Data from a prospective longitudinal cSLE cohort were used, with patient/parent consent. Patients were classified as cSLE by SLICC 2012 criteria with a disease onset < 18 years old. Definitions were: aLLDAS according to Franklyn (2), disease activity score by SLEDAI-2K, cLLDAS by cLSE T2T Task Force (Smith et al. submitted) and damage according to SLICC Damage Index. cLLDAS-50 was defined as attainment of cLLDAS in more than 50% of follow-up. Binary regression analysis was used for testing co-variates for attaining cLLDAS-50 with significance for p<0.05.

Results: 43 cSLE patients were studied, with a median age of symptom onset at 13.6 years, median age at diagnosis of 14.6 years and median follow-up of 4.6 years (range 1-13 years). Mean number of visits was 10.9 per patient. Mean SLEDAI at diagnosis was 15.4 (SD 10.4, range 2-43). Use of MMF was in 62.8%, AZA in 37.2%, and use of HCQ in 100% of patients. 41.9% of patients used a biologic (rituximab or belimumab) at any time point. Each patient reached aLLDAS and cLLDAS at least once during follow-up. Mean time to reach first aLLDAS/cLLDAS was 8.8 months and 9.7 months respectively. Only 58.1% (25/43) of patients were able to maintain cLLDAS-50. The use of biologic(s) had a inversely correlation on reaching cLLDAS-50 (p=0.005), but time to start biologic(s) was not taken into account. Shorter time to cLLDAS was correlated with attaining cLLDAS-50 (p=0.025). SLEDAI at diagnosis, renal/neurological disease and compliance problems were not correlated with attaining cLLDAS-50.

Conclusion: In a longitudinal cSLE cohort, reaching cLLDAS occurred later than aLLDAS, emphasizing the need for an adapted LLDAS definition for cSLE. This study shows that reaching cLLDAS in cSLE is feasible, but attaining cLLDAS-50 is difficult. Earlier starting of glucocorticoid-sparing drugs (such as biologics) seems necessary in a severe subgroup not retaining, or not reaching, cLLDAS.

REFERENCES:

[1] Holland et al. Measuring disease damage and its severity in childhood-onset systemic lupus erythematosus. Arthritis Care & Research Nov 2018; Vol. 70, No. 11: 1621-1629.
[2] Franklyn K et al. Definition and initial validation of a lupus low disease activity state (LLDAS). Ann Rheum Dis 2016;75:1615–21.
[3] Smith et al. Attainment of low disease activity and remission targets reduces the risk of severe flare and new damage in childhood lupus. Rheumatology 2022;61: 3378-3389.
[4] Wahadat et al. LLDAS is an attainable treat-to-target goal in childhood-onset SLE. Lupus Science & Medicine 2021;8:e000571. doi:10.1136.

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OP0036

FREQUENCY AND FACTORS ASSOCIATED WITH DIAGNOSTIC DELAY IN EUROPEAN PATIENTS WITH FAMILIAL MEDITERRANEAN FEVER: A STUDY ON 960 PATIENTS FROM THE JIR COHORT

Keywords: Innate immunity, Genetics/Epigenetics, Epidemiology

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Background: Familial Mediterranean fever (FMF) is the most common autoinflammatory disease worldwide. It affects mainly population from Mediterranean origin and is associated with *MEFV* exon 10 mutations. FMF is characterized by short and recurrent attacks of fever, abdominal or thoracic pain that lasts less than three days [1]. Several studies reported that FMF diagnosis may be missed or delayed even in countries with a high prevalence of the disease such Turkey and Israel but real causes explaining diagnostic delay in FMF are not totally elucidated.

Objectives: Our aim was to study a large cohort of European FMF patients to identify the frequency and associated factors of diagnosis delay.

Methods: Clinical data were extracted from the Juvenile Inflammatory Rheumatism (JIR)- cohort. All FMF patients fulfilled Livneh Criteria and had a sequencing of *MEFV* exon 10 available [2]. We defined FMF-diagnostic delay (d-FMF) as a duration between the onset of the symptoms and FMF diagnosis of more than 10 years.

Results: We enrolled 960 FMF patients; delayed diagnosis (d-FMF) was noted in 20% of patients (n=200) whereas 80% of other patients (FMF) (n=760) had the diagnosis made within the 10 years from the onset of symptoms. d-FMF patients were significantly older than other FMF with a median age of 46.4 years old versus 15.5 (p < 0.0001). Concerning women, the percentage of d-FMF was higher than other FMF patients (56% versus 47%, p=0.03). Regarding the clinical presentation during FMF attacks, the difference was not statistically significant on abdominal pain, musculoskeletal symptoms and chest pain. Only, erysipelas-like erythema was more frequently observed among d-FMF patients (33% versus 22%, p=0.0003). The percentage of patients with one or two pathogenic *MEFV* mutation was not different between d-FMF and other FMF patients. AA amyloidosis was significantly more frequent in d-FMF than FMF (10 % versus 2.6 %, p< 0.0001). As well, d-FMF patients received significantly more biotherapy compared to other FMF (18% versus 3.8%, p<0.0001).

Conclusion: Twenty percent of FMF patients were misdiagnosed before being officially diagnosed as FMF with significantly more women; this could be linked to the differential diagnosis of abdominal attacks with period pains, as frequently reported be women patients. Another clinical feature is erysipelas-like erythema which seems not be known as a pathognomonic symptom of FMF by all practitioners; this finding was previously reported in Israel and Turkey were the disease is however highly prevalent [4,5]. In conclusion, FMF delay is still significantly high nowadays. To our knowledge, our study is the first cohort study to investigate diagnostic wandering and the factors associated with long diagnostic wandering in a large European cohort. Education and better communication on this disease to patients and practitioners could be fruitful to improve FMF earlier diagnosis.

REFERENCES:

[1] Savey L, Grateau G, Georgin-Lavialle S. Fièvre méditerranéenne familiale en 2020. *Néphrologie & Thérapeutique* 2021;**17**:S119–25. doi:10.1016/j.nephro.2020.02.013
[2] Livneh A, Langevitz P, Zemer D, *et al.* Criteria for the diagnosis of familial mediterranean fever. *Arthritis & Rheumatism* 1997;**40**:1879–85. doi:10.1002/art.1780401023
[3] Lidar M, Tokov I, Chetrit A, *et al.* Diagnosis delay in familial Mediterranean fever (FMF): social and gender gaps disclosed. *Clin Exp Rheumatol* 2005;**23**:357–63.

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OP0037

ADHERENCE TO URATE-LOWERING THERAPY AFFECTS THE RISK OF CARDIOVASCULAR EVENTS IN PATIENTS WITH GOUT

Keywords: Cardiovascular disease, Real-world evidence, Gout

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