Other orphan diseases

AB1299 DIFFERENCES IN THE CLINICAL SPECTRUM OF HAPLOINSUFFICIENCY OF A20 (HA20) CASES DIAGNOSED DURING ADULTHOOD

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Background: Haploinsufficiency of A20 (HA20) is a monogenic autoinflammatory disease caused by heterozygous loss-of-function mutations in *TNFAIP3* gene and characterized by Behçet disease (BD)-like manifestations such as mucocutaneous, articular, gastrointestinal, ocular symptoms as well as recurrent fever, elevated acute-phase reactants during relapses; and it usually starts during early childhood. Autoimmunity is another component of HA20 with autoantibodies and variable clinical features resembling systemic lupus erythematosus (SLE) and other autoimmune diseases.
Objectives: We herein present three cases of HA20 with different clinical features and diagnosed during adulthood.
Methods: We used the Ion Torrent platform for deep sequencing.
Results: Case 1: A 51-year old woman diagnosed with BD because of oral and genital aphthous ulcers, arthralgias, erythema nodosum, and pathergy positivity starting from age of 40 in 2012. She developed sudden vision loss (diagnosed with bilateral optic neuropathy), sixth nerve palsy, and entrapment neuropathies in the lower limbs in 2014; and she had flares of neurologic findings between 2014-2020. The only laboratory abnormality was elevated acute-phase reactants, and no pathologic finding was reported for cranial MRI. Pathological examination of sural nerve biopsy revealed chronic inflammatory demyelinating polyneuropathy (CIDP). She received adalimumab and then tofacitinib, and her treatment was switched to certolizumab and IVIG (30 g/6 weeks) in 2020. At the last visit, she was asymptomatic with normal acute phase response, and her examination revealed normal eye movements.
Case 2: A 33-year old woman was followed for 12 years with the diagnosis of SLE, based on fever, photosensitivity, alopecia, polyarthritis, serositis, positive anti-nuclear antibody (ANA) at a titer of 1:1280 with a homogeneous pattern, positive anti-dsDNA, anti-Sm, anti-Sm/RNP, and lupus anticoagulant test, and leukopenia, lymphopenia, hypocomplementemia in 2008. She developed shrinking lung syndrome and Jaccoud arthropathy during the disease course. She received several drugs including corticosteroids, hydroxychloroquine, cyclophosphamide, mycophenolate mofetil, belimumab, rituximab, tocilizumab, abatacept, tofacitinib because of fever, arthritis, skin rash, increased acute-phase reactants, pancytopenia, anti-dsDNA positivity. Her fever, red arthritis attacks with high CRP values did not respond, and after the genetic diagnosis of HA20, anakinra was added to treatment. Due to the high dose anakinra requirement, her treatment was switched to canakinumab (150 mg/2 week), and at the last visit, her attacks were significantly reduced.
Case 3: A 44-year old woman was evaluated because of recurrent prolonged >38°C fever attacks (2 days-2 weeks duration), arthritis of the elbow, wrist, knee joints, and high acute phase reactant in 2004. She did not have a history of recurrent oral and genital aphthous ulcers, intermittent periorbital edema, rash, any ocular symptoms, or sensorineural hearing loss. ANA, RF, anti-CCP, and MEFV gene mutation were negative on admission. PET-CT demonstrated FDG uptake in the wall of the ascending aorta, aortic arch, and descending aorta in 2011. She had used colchicine in 2004, etanercept between 2009 and 2010, anakinra in 2011, tocilizumab in 2012, and canakinumab in 2013. She repeatedly received IV methylprednisolone pulse therapy, but she experienced a relapse of fever when she reduced the dose of methylprednisolone to <8 mg/day. Her knee arthritis did not respond to adalimumab, and she is currently on infliximab treatment since 2019 with a Daily methylprednisolone dose of 8-12 mg.
Conclusion: HA20 can be diagnosed even in adult patients, and the clinical picture of presented cases suggests that monogenic autoinflammatory disorders including HA20 should be suspected in any patient with flares of described manifestations along with strong acute phase response even in adults. Response to corticosteroids and targeted treatments may also be variable.
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Table 1: Characteristics of patients with A20 haploinsufficiency

	Case 1	Case 2	Case 3
Gender	Female	Female	Female
Family history	None	None	None
Systemic findings	Yes	Yes	Yes
Autoantibodies	None	Yes	None
High acute-phase reactants	Yes	Yes	Yes
Oral ulcers	Yes	Yes	No
Erythema nodosum	Yes	None	None
Genital ulcers	Yes	None	None
Uveitis	None	None	None
Arthritis	Yes	Yes	Yes
Neurologic involvement	Yes	None	None
Parenchymal involvement	None	None	None
Peripheral neuropathies	Yes	None	None
Current treatment	Certolizumab	Canakinumab	Infliximab
TNFAIP mutation	Arg697Lys	Thr647Pro	p.Phe40LeufsTer56

AB1300 AA AMYLOIDOSIS IN A PATIENT WITH MUTATIONS IN BOTH ADA2 AND A20 GENES

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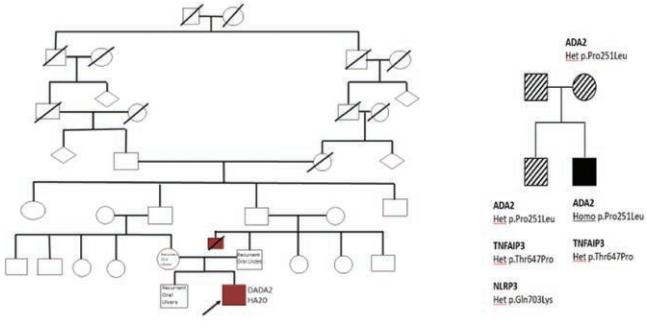
Background: Adenosine Deaminase 2 Deficiency (DADA2) and Haploinsufficiency of A20 (HA20) are two recently described monogenic autoinflammatory diseases (AID). The uncontrolled inflammatory response has been associated with an increased risk of AA amyloidosis in other AID, but there are only two reported patients with DADA2-related amyloidosis so far.[1,2]
Objectives: We herein report a patient with AA amyloidosis and AID associated with both DADA2 and HA20.
Methods: We used the Ion Torrent platform for deep sequencing.
Results: Case: A 20-year-old male patient born to consanguineous parents (Figure 1), was admitted to our hospital with fever and abdominal pain in June 2014. Peritonitis, hepatomegaly, and a palpable non-tender mass in the right axillary cavity were detected in physical examination, and his laboratory investigations revealed neutrophilic leukocytosis, high acute phase reactants (APR), and nephrotic range proteinuria. CT angiography showed multiple thrombotic microaneurysms in celiac, splenic, superior, and inferior mesenteric and bilateral renal arteries; and MRI documented an additional aneurysm in anterior communicating artery. No finding was detected in hepatitis serology. He had been diagnosed with polyarteritis nodosa, and prednisolone and azathioprine were started. Renal histopathology confirmed the AA amyloidosis. Genetic analysis revealed no pathogenic *MEFV* variant. Colchicine and anakinra 100 mg/day were added to his treatment. He experienced 1-2 abdominal episodes annually between 2014-2019, and APR were normal between attacks. In March 2019, he was admitted to the hospital because of abdominal pain, high APR, and iron deficiency anemia. No gross pathology was observed in endoscopic examination of gastrointestinal tract, but histopathological investigation of the gastric mucosa and terminal ileum showed AA amyloidosis. Multiple aneurysms were detected in renal arteries with angiography. Deep sequencing of the targeted genes revealed homozygous p.Pro251Leu in ADA2 gene and heterozygous p.Thr647Pro in TNFAIP3 gene encoding A20, confirming the molecular diagnosis of DADA2 and HA20. The patient described oral recurrent aphthous ulcers starting from his childhood, but he had no uveitis or genital ulcers. His mother and brother also had recurrent oral aphthous ulcers. Genetic analyses showed heterozygous p.Pro251Leu variant in ADA2 gene in his mother, and heterozygous p.Gln703Lys variant in NLRP3 gene as well as heterozygous p.Thr647Pro TNFAIP3 variant and heterozygous p.Pro251Leu ADA2 in his brother. An improvement in his findings was observed within 2 weeks after switching his anakinra to adalimumab 40 mg every other week. At his last visit in February 2021, the patient had no complaints with normal APR, and urinalysis analysis showed 200 mg/day proteinuria, which was regressed from 3 g/day.
Conclusion: This is the first case of AA amyloidosis associated with ADA2 and TNFAIP3 (A20) variants. ADA2 p.Pro251Leu variant has previously been validated as likely pathogenic, and our patient's clinical findings were mainly compatible with DADA2. On the other hand, TNFAIP3 gene p.Thr647Pro mutation has been reported as

Figure1: Pedigree of family and results of genetic analyses



variant of unknown significance, but it may have contributed to the DADA2 associated increased risk of amyloidosis. A better response of proteinuria to adalimumab treatment indicates superiority of anti-TNFs in DADA2 patients compared to anti-IL-1 drugs.

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AB1301 DETERMINING THE RELATIONSHIP BETWEEN SERUM INTERLEUKIN 33 LEVELS AND CLINICAL FEATURES OF THE DISEASE IN PATIENTS WITH FAMILIAL MEDITERRANEAN FEVER

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Background: Familial Mediterranean Fever (FMF) is an autoinflammatory disease characterized by recurrent fever, serositis, arthritis and erysipelas-like erythema caused by mutations over activating caspase-1. As Interleukin (IL)-1 beta, IL-33 is a nuclear cytokine from IL-1 family which is activated by caspase-1. IL-33 is known to take part in pathogenesis of several rheumatic diseases.

Objectives: The aim of this research is determining the relationship between serum IL-33 levels and clinical features of the disease in patients with FMF disease.

Methods: The research involved 54 FMF patients and 29 healthy volunteers. Serum IL-33 levels were evaluated in both patients and healthy individuals, and its relationship between clinical and laboratory features of FMF.

Results: 28 out of 54 patients (%51.8) had favorable response to colchicine while 26 patients (%48.2) had colchicine resistant disease. FMF patients had lower IL-33 levels compared to healthy control group (p= 0.06). There were no difference between colchicine responsive and resistant patients (p=0.12) and no association was found between clinical features and serum IL-33 levels. Additionally, IL-33 did not correlated with C-reactive protein and disease activity assessed by autoinflammatory disease activity index.

Conclusion: No association was found between serum IL-33 levels and FMF disease features and laboratory findings. This may be due to the small size of our patient group, the involvement of IL-33 in tissue homeostasis as well as inflammation, and the use of higher doses of colchicine in the resistant disease group than in the remission group. Additional research is needed to determine IL-33's role in FMF pathogenesis and its relationship with clinical and laboratory features.

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AB1302 EVALUATING THE CLINICAL UTILITY OF PATIENT ACCEPTABLE SYMPTOM STATE IN PATIENTS WITH FAMILIAL MEDITERRANEAN FEVER

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Background: Familial Mediterranean Fever (FMF) is an autoinflammatory disease characterized by recurrent attacks of fever, serositis, arthritis and erysipelas-like erythema. Patient acceptable symptom state (PASS) is a disease evaluation method to assess disease activity with a simple question especially in rheumatic diseases.

Objectives: We aimed to investigate clinical utility of PASS in FMF patients.

Methods: The research involved 54 FMF patients. Patient acceptable symptom state was applied to all patients in the study. The answers to PASS were compared with the patients clinical and laboratory features.

Results: 28 out of 54 patients (51.8%) were colchicine responsive whereas, 26 patients (48.2%) had colchicine resistant disease. The number of patients who answered yes to PASS (I'm happy with my current disease condition) was 32 (59%), while answered no (I need further treatment options) was 22 (41%). Considering the disease severity assessed with International severity scoring FMF (ISSF) of those who answered yes, 22 (68%) patients had mild disease, 10 patients had moderate (32%) disease, and there was no patient with severe disease in this group. Among those who answered no, 3 (14%) had mild disease, 14 (63%) had moderate disease, and 5 (23%) had severe disease (p <0.001). When the CRP levels of the patients were compared, the median CRP value of those who answered yes was found to be 4.45 mg/L, and the median value of CRP for those who answered no was 11.25 mg/L (p= 0.04).

Sensitivity and specificity of PASS for detecting patients in remission was 78% and 61% respectively. Moreover, PASS had a positive and negative predictive value of %68 and %72 respectively, for determining patients in remission. If cut off level of CRP was chosen as 6.5 mg/L for answering "yes" to PASS, sensitivity of test has been found to be 62.5% while the specificity is 59.1%. On the other hand, if cut off level of CRP is selected as 9.35 mg/L; sensitivity and specificity of the test was found as 75% and 72.7% respectively (p=0.045).

Conclusion: Patient acceptable symptom state is found beneficial in evulation these patients simply and swiftly especially in terms of distinguishing severe FMF disease. In FMF, laboratory remission is as important as clinical remission, therefore, PASS by alone, is not sufficient for making treatment decisions and should be supported by inflammatory markers.

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AB1303 VACCINATION PRACTICES OF ADULT FAMILIAL MEDITERRANEAN FEVER PATIENTS IN TURKEY.

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Background: Vaccines are the safest and most effective method to prevent invasive and life-threatening infections. Vaccines against influenza, pneumococcal disease, herpes zoster, and human papillomavirus are the main recommended vaccines for adults. In addition, rheumatology patients are advised to receive adult vaccinations according to the vaccines available in their country and local guidelines. In Turkey, both influenza and pneumococcal disease vaccines are commercially available. In addition, these vaccines are strongly recommended for rheumatology patients in local guidelines. Although familial Mediterranean fever (FMF) is one of the most common rheumatological diseases in Turkey, it is often neglected in vaccination recommendations.

Objectives: In this study, we surveyed the vaccination practice against influenza or pneumococcal diseases of adult FMF patients in our cohort. In addition, we evaluated the factors related to favorable vaccination practice.

Methods: We included 360 FMF patients over 18 years of age. All patients fulfilled the Tel-Hashomer criteria for FMF. We asked them if they had ever been vaccinated against pneumococcal or influenza, and how often they received them. In addition, we dichotomised patients in terms of vaccinated against at least one of influenza or pneumococcal diseases. We then compared the groups for demographic (age gender and comorbidities) and disease related characteristics (disease duration, disease activity calculated by ISSF and colchicine dose). We used qi-square test to compare categorial variables and Mann-Whitney U test to compare continuous variables. P<0.05 was accepted as significant.

Results: Of 360 FMF patients, 238 (66.1%) were female. The mean age of the patients was 34.5±10.7 years. Disease duration of the patients was 9.38±0.7 years. In addition, the mean ISSF score of the patients was 1.83±1.5. The mean dose of colchicine received by the patient was 1.23 ± 0.47 mg. Only 54 (15.0%) of the patients had at least one comorbidity. In our cohort, 22 (6.1%) patients were vaccinated against influenza or pneumococcal disease. Only 18 (5.0%) of the patients have been vaccinated against influenza at least once so far. Half of these patients (9/18) were vaccinated against influenza each year. In addition, 8/360 (2.2%) patients were fully vaccinated against pneumococcal diseases. Here, six of them received the pneumococcal vaccine after the start of the COVID-19 outbreak. There was no statistically significant difference between the groups in terms of demographic and disease related characteristics.

Conclusion: We found that vaccination practice of FMF patients in our cohort was unsatisfactory. Few patients follow adult vaccination recommendations. In addition, clinicians should be concerned about the importance of vaccination and guide their patients to get the adult vaccines available in their country.