- [2] Neel A., Henry B., Barbarot S. et al. Long-term effectiveness and safety of interleukin-1 receptor antagonist (anakinra) in Schnitzler syndrome: a french multicenter study Autoimmunity. Reviews. 2014;13:1035-1041
- [3] Krause K., Tsianakas A., Wagner N. et al. Efficacy and safety of canakinumab in Schnitzler syndrome: a multicenter randomized placebo-controlled study. 2017; J Allergy Clin Immunol 2017;139:1311-20.

Disclosure of Interests: None declared
DOI: 10.1136/annrheumdis-2019-eular.4611

AB1103 NEUROLOGICAL IMPAIRMENT DURING SARCOIDOSIS

sameh sayhi¹, Rim Dhahri¹, Najah Boussetta¹, Bilel Arfaoui¹, Feida Laajili², Bassem Louzir¹, Hajer Derbali³, Linda Mrisa³, Ridha Mrisa³. ¹Military Hospital of Tunis Tunisia, Internal Medicine, Tunis, Tunisia; ²Military Hospital of Tunis Tunisia, Autoimmune Diseases Unit Research UR17DN02, Tunis, Tunisia; ³Military Hospital of Tunis Tunisia, Neurology, Tunis, Tunisia

Background:

Objectives: To describe neurological impairment characteristics in sarcoidosis.

Methods: This was a descriptive and retrospective study including 65 patients with sarcoidosis, followed in the departments of internal medicine and neurology at the Military Hospital of Tunis over a period of 20 years from 1997 to 2017.

Results: A total of 65 patient files have been selected, of which 38 have neurological involvement.

Thirty-eight patients met the inclusion criteria for Neurosarcoidosis. According to Zajicek's criteria, the diagnosis of neurosarcoidosis was certain in 2 cases, probable in 18 cases and possible in 18 cases.

Neurological disorders were symptomatic in 58.5% of the studied population. Neurological signs were inaugural in 9 patients (14% of cases). A central neurological involvement was demonstrated in 33 patients (86.8%), the peripheral nervous system was affected in 5 patients (13.1%), and cranial nerve involvement was found in 10 patients (26.3%). Ten patients have had both central and peripheral impairment.

Neurological involvement was significantly associated with cardiac, renal extra-thoracic, ophthalmologic, articular and cutaneous involvement (p <0.05)

Genotyping of the conversion enzyme and HLA typing did not show any particular pattern of neurosarcoidosis in comparison with patients without neurological signs.

Conclusion: Neurological impairment was frequently observed in our series. It was also significantly associated with multivisceral involvement without particular genetic pattern.

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2019-eular.7883

AB1104 GENETIC ASPECTS OF SARCOIDOSIS IN A TUNISIAN POPULATION

sameh sayhi¹, Rim Dhahri¹, Najah Boussetta¹, Souha Hannachi¹, Feida Laajili², Bassem Louzir¹, Hajer Derbali³, Linda Mrisa³, Ridha Mrisa³. ¹Military Hospital of Tunis Tunisia, Internal Medicine, Tunis, Tunisia; ²Military Hospital of Tunis Tunisia, Autoimmune Diseases Unit Research UR17DN02, Tunis, Tunisia; ³Military Hospital of Tunis Tunisia, Neurology, Tunis, Tunisia

Background:

Objectives: To determine the frequencies of the HLA alleles and genotypes of the ACE gene.

Methods: This is a cross sectional study of 65 patients with sarcoidosis, followed in the departments of internal medicine and neurology at the Military Hospital of Tunis. The genetic study involved only 50 patients. DNA extraction was performed to determine the frequencies of the HLA alleles and genotypes of the ACE gene.

Results: 1. HLA typing

The analysis of HLA typing allowed us to estimate the different frequencies of alleles in patients. The calculation of the allelic frequency found that the most frequent alleles are HLA-DRB1 * 1501 alleles with a frequency of 38% and HLA-DRB1 * 0301 of 28%. Other alleles are at lower frequencies (Table1).

HLA	N	%
N=50		
HLA-DRB1*1501	19	38%
HLA-DRB1*0301	14	28%
HLA-DRB1*1106	9	18%
HLA-DRB1*0401	8	16%

2. Genotyping of the ECA gene

Genotyping of the polymorphism of the angiotensin converting enzyme (ACE) involved 50 patients. Genotypic frequencies (II, ID and DD) and allele frequencies (I and D) were estimated in order to evaluate the frequencies of each genotype and the 2 alleles for this pathology. The genotypic and allelic frequency results were summarized in Table 2.

Genotypes	N	%
II	11	22%
ID	24	48%
DD	15	30%
Alleles		
I	46	46%
D	54	54%

Conclusion: The most frequent alleles in Tunisian patients with sarcoidosis are HLA-DRB1 * 1501 alleles with a frequency of 38% and HLA-DRB1 * 0301 of 28%. The genotypic and allelic results showed that genotype ID was the most frequent with 48% with a predominance of the D allele in 54%.

References:

DISCLOSURE OF INTERESTS

None declared

DOI: 10.1136/annrheumdis-2019-eular.7967

AB1105 A NOVEL AUTOINFLAMMATORY AND LYMPHOPROLIFERATIVE SYNDROME ASSOCIATED WITH PIM1 MUTATIONS

Giovanna Ferrara¹, Silvio Polizzi², Erica Valencic³, Annalisa Chiochetti⁴, Josef Vuch³, Alessia Pin¹, Elisa Piscianz¹, Diego Vozzi³, Serena Pastore³, Paola Tomietto⁵, Andrea Taddio⁶, Flavio Faletta³, Umberto Dianzani⁴, Alberto Tommasini³. ¹University of Trieste, Trieste, Italy; ²Meyer Children's Hospital, Trieste, Italy; ³Institute of Maternal and Child Health, IRCCS Burlo Garofolo, Trieste, Italy; ⁴Università del Piemonte Orientale, Novara, Italy; ⁵Azienda Sanitaria Universitaria Integrata Trieste, Cattinara Teaching Hospital, Trieste, Italy; ⁶Institute of Maternal and Child Health, IRCCS Burlo Garofolo and University of Trieste, Trieste, Italy

Background: Whole exome sequencing can allow genetic diagnosis in subjects with long lasting clinical stories not supporting any well-defined disorder.

A 35-year-old man was referred to ophthalmologist's evaluation for blurry vision in his left eye. The fundus examination showed choroidal lesions in both eyes. His past medical history was relevant for celiac disease, recurrent episodes of fever and skin rashes with leukocytoclastic vasculitis, inflammatory lesions of the osteoarticular and muscular system, one episode of aseptic meningitis, an intracranial granuloma and two episodes of anterior uveitis. He had also splenomegaly with non-caseating granulomas. Brain TC founded multiple lytic and sclerotic skull lesions. He was diagnosed with atypical sarcoidosis and treated with oral steroid and methotrexate.

Laboratory data always showed elevated erythrocyte sedimentation rate, strong positive C-reactive protein and polyclonal gammopathy.

Objectives: To describe functional and genetic data supporting the role of a PIM1 mutation in the multisystemic inflammation and lymphoproliferation of the patient.

Methods: Whole exome sequencing (WES) analysis. Flow-cytometry to evaluate Pim1 expression, Bad phosphorylation (target of Pim1 kinase) and the effect of PIM inhibitor on peripheral blood mononuclear cell (PBMC) viability. RNAseq was on primary fibroblasts from the patient and

from healthy donors. Cloning of the mutated gene in a vector for further functional studies.

Results: WES analysis revealed the de novo heterozygous missense variation c.C1132A (p.H378N) in *PIM1* gene. This variation was never described in on-line database and was predicted as damaging by various bioinformatic tools. Preliminary functional investigations in fibroblasts showed normal expression of Pim1, but higher phosphorylation of BAD protein was measured in cells from the patient. Moreover, PBMC from the patient displayed a lower sensitivity to the PIM inhibitor PIM447. RNAseq showed an altered expression profile in genes involved in the extracellular matrix organization.

Conclusion: PIM1 is an oncogene that encodes a protein kinase and, indeed, somatic gain of function mutations can be found in cancers. Preliminary data obtained from our patient suggest a gain of function effect of the p.H378N variant. The lymphoproliferative disorder may be sustained by the anti-apoptotic action of phosphorylated BAD. Recent data correlated hyperactive PIM1 in tumors with high degree of inflammatory infiltration accompanied by NFAT and mTOR activation and IL6 expression. A role of this cytokine also in our patient was coherent with a good clinical response to a treatment with tocilizumab, targeting IL-6.

Although these results are supportive of a role of mutated PIM1 in the observed phenotype, we cannot still claim that this is causative of a novel syndrome. The detection of further cases and functional studies on cells transfected with mutated PIM1 will help shedding more light on this inflammatory and lymphoproliferative disorder.

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2019-eular.8060

AB1106

PREVALENCE AND EPIDEMIOLOGY OF FAMILIAL MEDITERRANEAN FEVER AND TUMOR NECROSIS FACTOR RECEPTOR-ASSOCIATED PERIODIC SYNDROME: RESULTS FROM AN ITALIAN CENTER

Rossella Talotta¹, Lorena Mosca², Francesco Rucci¹, Antonio Brucato³, Fabiola Atzeni⁴, Carlo Federico Perno⁵, Francesco Scaglione⁶, Ugo Cavallari².

¹University of Milan, Postgraduate School of Clinical Pharmacology and Toxicology, Milan, Italy; ²ASST Grande Ospedale Metropolitano Niguarda, Medical Genetics Unit, Department of Laboratory Medicine, Milan, Italy; ³Papa Giovanni XXIII Hospital, Internal Medicine Unit, Bergamo, Italy; ⁴University of Messina, Rheumatology Unit, Messina, Italy; ⁵ASST Grande Ospedale Metropolitano Niguarda, Chemical-Clinical Analysis and Microbiology, Department of Laboratory Medicine, Milan, Italy; ⁶University of Milan, Department of Oncology and Onco-Hematology, Milan, Italy

Background: Familial Mediterranean fever (FMF) and tumor necrosis factor (TNF) receptor-associated periodic syndrome (TRAPS) represent two forms of periodic monogenic autoinflammatory diseases, characterized by recurrent and auto-limiting attacks of fever and systemic inflammation. Both the diseases are due to the aberrant activation of inflammasome platforms. Several variants in the *Mediterranean Fever (MEFV)* gene and *TNF Receptor Superfamily Member 1A (TNFRSF1A)* gene are respectively at the basis of FMF and TRAPS.

Objectives: The aim of this study is to report the genotype and phenotype prevalence of a cohort of patients referring to our laboratory with a suspicious diagnosis of FMF or TRAPS.

Methods: We retrospectively collected genetic and demographic data of patients undergoing *MEFV* (NM_000243) and *TNFRSF1A* (NM_001065) genetic test at our laboratory. Both genes were analysed by direct sequencing on both strands. Data were statistically analysed for descriptive and inferential purposes.

Results: A total of 168 cases were collected, most of which were Caucasian subjects (88.0%). The most common clinical manifestation was periodic fever, occurring in 121 cases, with musculoskeletal, intestinal and cutaneous symptoms, polyserositis and lymphadenopathy occurring at variable rates. Demographic and clinical characteristics are resumed in *tab.1*. *MEFV* genotyping, performed in 159 patients, identified 8 different pathogenic variants (p.Phe479Leu, p.Met680Ile, p.Met694Val, p.Met694Ile, p.Lys695Arg, p.Val726Ala, p.Ala744Ser, p. Arg761His), associated with different geographic provenience and symptoms (*tab.2, 4*).

Analysis of *TNFRSF1A* gene in 80 subjects revealed the presence of the pathogenic variant p.Cys102Tyr in 3 patients (3.75%); *tab.3, 5*. According to Eurofever scoring system, the *MEFV* variant p.Ala744Ser was significantly associated to the likelihood of having FMF and to the severity of the disease. A higher prevalence of *MEFV* pathogenic variants was observed in Egyptians and patients living in Southern Italy.

Patients n. 168	
Age, years (mean±SD)	39.9 ± 18.0
Age at disease onset, years (mean±SD)	25.8 ± 16.3
Gender [females/males; n.(%)]	94(56.0%)/74(44.0%)
Periodic fever, n.(%)	121 (72.0%)
Musculoskeletal symptoms, n.(%)	72 (42.9%)
Cutaneous rash, n.(%)	14 (8.3%)
Eye involvement, n.(%)	4 (2.4%)
Oral aphthosis, n.(%)	19 (11.3%)
Spleen enlargement, n.(%)	4 (2.4%)
Hepatomegaly, n.(%)	6 (3.6%)
Lymphadenopathy, n.(%)	34 (20.2%)
Intestinal symptoms, n.(%)	77 (45.8%)
Pericarditis, n.(%)	39 (23.2%)
Peritonitis, n.(%)	10 (6.0%)
Pleuritis, n.(%)	22 (13.1%)
Pharyngodynia, n.(%)	23 (13.7%)
Familial history, n.(%)	22 (13.1%)
NSAIDs, n.(%)	27 (16.1%)
Steroids, n.(%)	36 (21.4%)
Colchicine, n.(%)	35 (20.8%)
Immunosuppressants, n.(%)	12 (7.1%)

Table 1. Demographic characteristics of the whole cohort of patients examined.

Variant	Amino acid Change	rs Code	Exon	Clinical Significance	Wild Type Patients, n. (%)	Heterozygous Carriers, n. (%)	Homozygous Carriers, n. (%)	Missing Subjects, n. (%)
c.306T>C	p.Asp102>	rs224225*	2	Benign	52 (33.1%)	49 (31.2%)	25 (15.9%)	31 (19.7%)
c.414A>G or T	p.Gly138>	rs224224*	2	Benign	53 (33.8%)	48 (30.6%)	25 (15.9%)	31 (19.7%)
c.440G>C	p.Glu148Gln	rs3743930	2	Uncertain	147 (93.6%)	10 (6.4%)	0 (0%)	0 (0%)
c.495C>A	p.Ala165>	rs224223*	2	Benign	49 (31.2%)	52 (33.1%)	25 (15.9%)	31 (19.7%)
c.605G>	p.Arg202Gln	rs224222*	2	Benign	82 (52.2%)	38 (24.2%)	7 (4.5%)	30 (18.1%)
c.804A>G	p.Asn270Asp	/	2	Other	155 (98.7%)	2 (1.3%)	0 (0%)	0 (0%)
c.866C>T	p.Ala289Val	rs104895132	2	Uncertain significance	156 (99.4%)	1 (0.6%)	0 (0%)	0 (0%)
c.942C>T	p.Arg314>	rs224211*	3	Benign	81 (51.7%)	61 (38.9%)	34 (21.7%)	31 (19.7%)
c.1105C>T	p.Pro369Ser	rs11466023	3	Other	156 (99.4%)	1 (0.6%)	0 (0%)	0 (0%)
c.1322G>A	p.Arg441Gln	/	4	/	156 (99.4%)	1 (0.6%)	0 (0%)	0 (0%)
c.1422G>A	p.Glu474>	rs224208*	5	Benign	34 (21.7%)	55 (35.0%)	37 (23.6%)	31 (19.7%)
c.1428A>G	p.Gln476>	rs224207*	5	Benign	34 (21.7%)	55 (35.0%)	37 (23.6%)	31 (19.7%)
c.1437 C>G or A	p.Phe479Leu	rs104895083	5	Pathogenic	150 (95.5%)	2 (1.3%)	0 (0%)	0 (0%)
c.1503C>T	p.Arg501>	rs76464258	5	Benign	156 (99.4%)	1 (0.6%)	0 (0%)	0 (0%)
c.1518 C>T	p.Ile506>	rs104895099	5	Likely benign	156 (99.4%)	1 (0.6%)	0 (0%)	0 (0%)
c.1530T>C	p.Asp510>	rs224206*	5	Benign	36 (22.9%)	54 (34.4%)	36 (22.9%)	31 (19.7%)
c.1764G>A	p.Pro588>	rs1231122*	9	Benign	40 (25.5%)	58 (36.9%)	29 (18.5%)	30 (18.1%)
c.1772T>C	p.Ile591Thr	rs11466045	9	Other	154 (98.1%)	1 (1.9%)	0 (0%)	0 (0%)
c.1818C>G or T	p.Trh606>	rs10489521	10	Unstested	156 (99.4%)	1 (0.6%)	0 (0%)	0 (0%)
c.2040G>A	p.Met680Ile	rs28940580	10	Pathogenic	149 (94.9%)	7 (4.5%)	1 (0.6%)	0 (0%)
c.2080A>G	p.Met694Val	rs61752717	10	Pathogenic	149 (94.9%)	8 (5.1%)	0 (0%)	0 (0%)
c.2085G>A	p.Met680Ile	rs28940578	10	Pathogenic	151 (96.2%)	6 (3.8%)	0 (0%)	0 (0%)
c.2084A>G	p.Lys695Arg	rs104895094	10	Pathogenic	154 (98.1%)	3 (1.9%)	0 (0%)	0 (0%)
c.2118G>A	p.Pro706>	rs2234939	10	Likely benign	155 (98.7%)	2 (1.3%)	0 (0%)	0 (0%)
c.2377T>C	p.Val726Ala	rs28940579	10	Pathogenic	150 (95.5%)	7 (4.5%)	0 (0%)	0 (0%)
c.2390G>T	p.Ala744Ser	rs61732474	10	Pathogenic	154 (98.1%)	3 (1.9%)	0 (0%)	0 (0%)
c.2282G>A	p.Arg761His	rs104895097	10	Pathogenic	155 (98.7%)	2 (1.3%)	0 (0%)	0 (0%)

Table 2. Variants identified in *MEFV* gene (NM_000243).

Variant	Amino acid Change	rs Code	Exon	Clinical Significance	Wild Type Patients, n. (%)	Heterozygous Carriers, n. (%)	Homozygous Carriers, n. (%)	Missing Subjects, n. (%)
c.36A>G	p.Pro12>	rs767455*	1	Benign	17 (20.5%)	38 (45.8%)	15 (18.1%)	13 (15.7%)
c.305 G>A	p.Cys102Tyr	/	3	Likely pathogenic	82 (98.8%)	1 (1.2%)	0 (0%)	0 (0%)
c.362G>A	p.Arg121Gln	rs14149584	4	Uncertain	81 (97.6%)	2 (2.4%)	0 (0%)	0 (0%)
c.369C>T	p.Trh123>	rs104895260	4	Uncertain	82 (98.8%)	1 (1.2%)	0 (0%)	0 (0%)

Table 3. Variants identified in *TNFRSF1A* gene (NM_001065).