Epidemiology and Characteristics of Sarcoidosis Across Diverse Ethnic Groups in Israel

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ABSTRACT **Background:** Sarcoidosis is a multi-organ granulomatous inflammatory disease of unknown etiology, exhibiting significant regional and ethnic variability in disease extent and clinical features.

Objectives: To investigate the clinical characteristics of sarcoidosis among Jewish and Arab populations in Israel and to compare these findings with global data.

Methods: We conducted a retrospective review on sarcoidosis patients at Rambam Health Care Campus during 2015–2023. Patients were categorized by ethnicity. Their demographic and clinical data were collected and analysed using appropriate statistical methods.

Results: The study included 284 patients (149 Jewish, 135 Arab). Jewish patients had a higher mean age at diagnosis. Diagnosis was biopsy-proven in 82% of cases, with endobronchial ultrasound being the most common diagnostic procedure. Lung involvement was present in 88% of patients, with no significant difference between Jewish and Arab populations. No significant differences were found in pulmonary function tests, blood tests, or Scadding stage distribution between the ethnic groups. When comparing the Jewish and Arab populations to the global data, lung involvement was significantly less frequent in the Jewish population. The Israeli population, both Jewish and Arab populations, had a significantly higher rate of joint manifestations whereas eye and skin manifestations appeared to be significantly lower in the Israeli population compared to global data.

Conclusion: This study highlights the diverse clinical presentations of sarcoidosis among Israeli populations compared to world data, with notable differences between Jewish and Arab patients, and within subgroups of these populations.

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KEY WORDS: Arab, Israel, Jewish, sarcoidosis

Sarcoidosis is a systemic, multi-organ, granulomatous inflammatory disease of unknown etiology. Even nearly 150 years since its first description, sarcoidosis remains an enigmatic disease with unknown causes and a wide spectrum of severity, ranging from mild asymptomatic conditions to disabling and life-threatening illness. Environmental exposure and genetic susceptibility have been proposed as the leading causes for disease development [1]. The disease spectrum of diversity is impacted by regions and populations, as evidenced by the high annual incidence of sarcoidosis observed in northern European countries (5–40 cases per 100,000 people) [2] and various differences among ethnic and racial groups as seen in the adjusted annual incidence in African Americans, which is roughly three times more than in Caucasian Americans (35.5 cases per 100,000 vs. 10.9 per 100,000, respectively) [3]. Sarcoidosis is also more likely to be chronic and fatal among African Americans [4-6].

While the diversity of sarcoidosis in terms of epidemiology and clinical presentation has been extensively studied worldwide [7,8], there is a lack of data for the Israeli population. Few studies have examined cohorts within Israel. Markevitz et al. [9] conducted a retrospective review of the clinical outcomes and organ involvement in 166 sarcoidosis patients in Israel. The authors found relatively similar disease presentation to world data with some local disease extent modifications. When considering the diversity of disease characteristics amongst different ethnic groups in Israel, particularly the Jewish and Arab populations, information was limited to a single study by Yigla et al. [10], which included data dating back more than three decades that described different forms of presentation, clinical manifestation, severity, and prognosis of sarcoidosis in patients of Arabic and Jewish origin. Several studies have demonstrated ethnic differences and

disparities in other medical conditions between the Jewish and Arab populations in Israel [11-13].

In our study, we shed light on the ethnic diversity among the Israeli Arab and Jewish populations while comparing these findings to global sarcoidosis population data [14]. We identified distinct patterns of organ involvement or disease presentation in Jewish and Arab patients that could potentially lead to a more personalized screening and treatment strategies.

PATIENTS AND METHODS

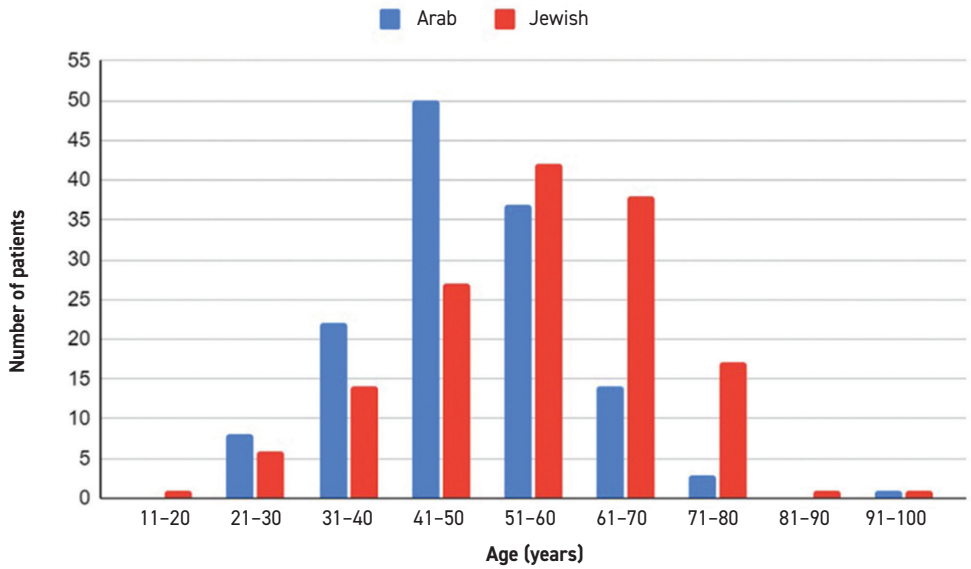
We retrospectively collected data on all patients diagnosed with sarcoidosis who visited Rambam Health Care Campus during 2015–2023. The study population was divided into two main groups based on ethnic origin: Jews and Arabs. In addition, we made a sub-division analysis for the Arab population in terms of religion (Christians vs. Muslims) and in the Jewish population in terms of its special ethnicity (Ashkenazi vs. Sephardi). Demographic and clinical parameters specific to sarcoidosis were collected and the following categories were evaluated:

- **Demographic data:** sex, age at diagnosis, place of birth, ethnic origin, smoking status, and co-morbidities
- **Mode of diagnosis:** procedure used to obtain a histologic specimen, including endobronchial ultrasound (EBUS), mediastinoscopy, trans-bronchial biopsy (TBB), liver biopsy, needle biopsy, bone marrow biopsy, skin biopsy, and clinical diagnosis
- **Disease features:**
  - *Clinical features:* organ involvement
  - *Pulmonary Function test (PFT)*
  - *Blood tests:* complete blood count, kidney function tests, liver function tests, blood serum calcium, angiotensin-converting enzyme, vitamin D and vitamin D 1,25-dihydroxy, C-reactive protein, erythrocyte sedimentation rate
- **Imaging:** X-ray, Scadding stages, computed tomography of the chest
- **Therapy:** number of patients treated, treatment type, duration
- **Outcomes:** curation of follow-up, remission, death

STATISTICS

Standard descriptive statistics were used to summarize population characteristics. We used a chi-square test for categorical variables, Mann-Witney U test for nonparametric variables, and Student's unpaired *t*-test for normally distributed continuous variables. Tukey's correction was applied when applicable to adjust for multiple comparisons. Categorical variables were described using proportions and percentages, non-parametric variables using median and interquartile range (IQR), and normally distributed continuous variables by means ± standard deviation. A 2-sided $P < 0.05$ was considered statistically significant for all tests. Statistical analyses were performed using R Statistical Software, version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria).

Figure 1. Distribution of age at diagnosis



RESULTS

Our study included a total of 300 patients, of whom 284 were included in the comparative analysis between Jewish (n=149; 79 females, 70 males) and Arab (n=135; 49 females, 86 males) patients. The mean age at diagnosis was significantly higher for the Jewish population as compared to the Arab population (57 vs. 47 years, respectively, $P < 0.0001$) [Figure 1]. A male predominance was observed in the Arab population, which is atypical as compared to the global gender distribution data of sarcoidosis. The most prevalent co-morbidities in both populations were cardiovascular and metabolic disorders, particularly diabetes mellitus. A history of smoking was reported in 25% of the patients, with a higher prevalence, yet not significant, among the Arab population, consistent with data from the general population [Table 1].

MODE OF DIAGNOSIS

Overall, 82% (n=233) of the patients had a biopsy-proven diagnosis of sarcoidosis. The most common diagnostic procedure was EBUS (n=81, 29%), followed by mediastinoscopy (n=49, 17%) and TBB (n=44, 15%). The rest of the biopsy-proven patients (N=59, 20%) were diagnosed by various other diagnostic procedures (e.g., CT-guided FNA/FNB, skin biopsy, liver biopsy, bone marrow biopsy). There was no significant difference between the Arab and Jewish population regarding the diagnostic procedures used. In 18% (n=51) of the total population, no biopsy was performed, and the diagnosis was based on clinical features and typical radiographic findings consistent with sarcoidosis. Within this group of clinical diagnosis, there was a predominance of Jewish patients (24% vs. 11%, respectively, $P = 0.0042$).

DISEASE SPECIFIC FEATURES

Data on organ involvement showed that 88% of patients had lung involvement. Multi-organ involvement was present in 32% of patients, with similar rates observed in the Arab and Jewish populations. Hypercalcemia was observed exclusively in the Jewish population (7%). Other organ involvement patterns were comparable between the two groups. In a sub-analysis of the Jewish population, lung involvement was significantly more prominent in Ashkenazi patients than in Sephardi patients (94% vs. 74%, respectively, $P = 0.046$). Conversely, joint involvement was more prevalent in the Sephardi group (14% vs. 2%, respectively, $P = 0.024$). No significant differences were observed in a similar sub-analysis of the Arab population between Christians and Muslims [Table 2].

Table 1. Population demographics and characteristics

Characteristic	Overall, N=284*	Arab, n=135*	Jewish, n=149*	*P*-value**
Age, years	52 (43–61)	47 (41–54)	57 (48–64)	**< 0.0001**
Female	128 (45%)	49 (36%)	79 (53%)	**0.0047**
Male	156 (95%)	86 (64%)	70 (47%)	
Co-morbidities				
Metabolic	40 (14%)	22 (16%)	18 (12%)	0.31
Cardiovascular	41 (14%)	16 (12%)	25 (17%)	0.24
Malignancy	17 (6.0%)	5 (3.7%)	12 (8.1%)	0.12
Other pulmonary	10 (3.5%)	5 (3.7%)	5 (3.4%)	> 0.99
Autoimmune	9 (3.2%)	5 (3.7%)	4 (2.7%)	0.74
Other	10 (3.5%)	3 (2.2%)	7 (4.7%)	0.34
Smoking history	72 (25%)	44 (33%)	28 (19%)	**0.032**
Residency				
Rural	118 (42%)	94 (70%)	24 (16%)	**< 0.0001**
Urban	165 (58%)	41 (30%)	124 (83%)	

*Total for each population
**Significance of the difference between Arab and Jewish per each variable
Bold signifies statistical significance

Table 2. Disease specific features

	Overall, N=284*	Arab, n=135*	Jewish, n=149*	*P*-value**
Organ involvement				
Lungs	250 (88%)	124 (92%)	126 (85%)	0·059
Liver/ gastrointestinal	25 (8.8%)	11 (8.1%)	14 (9.4%)	0·71
Joints	24 (8.5%)	12 (8.9%)	12 (8.1%)	0·80
Skin	21 (7.4%)	6 (4.4%)	15 (10%)	0·071
Eyes	14 (4.9%)	4 (3.0%)	10 (6.7%)	0·15
Cardiac	12 (4.2%)	6 (4.4%)	6 (4.0%)	0·86
Hypercalcemia	10 (3.5%)	0 (0%)	10 (6.7%)	**0·0019**
B symptoms	8 (2.8%)	4 (3.0%)	4 (2.7%)	> 0.99
Bone	7 (2.5%)	2 (1.5%)	5 (3.4%)	0·45
Central nervous system	6 (2.1%)	1 (0.7%)	5 (3.4%)	0·22
Kidneys	5 (1.8%)	3 (2.2%)	2 (1.3%)	0·67
Upper respiratory	5 (1.8%)	2 (1.5%)	3 (2.0%)	> 0.99
Bone marrow	4 (1.4%)	1 (0.7%)	3 (2.0%)	0·62
Other	10 (3.5%)	6 (4.4%)	4 (2.7%)	0·53
Multiple organ involvement	92 (32%)	40 (30%)	52 (35%)	0.34
Scadding grade				
0	20 (7.0%)	5 (3.7%)	15 (10%)	0.21
1	126 (44%)	65 (48%)	61 (41%)	
2	116 (41%)	55 (41%)	61 (41%)	
3	9 (3.2%)	3 (2.2%)	6 (4.0%)	
4	13 (4.6%)	7 (5.2%)	6 (4.0%)	
Treatment				
Prednisone	105 (37%)	50 (37%)	55 (37%)	0.98
Methotrexate	21 (7.4%)	5 (3.7%)	16 (11%)	**0.024**
Plaquenil	13 (4.6%)	5 (3.7%)	8 (5.4%)	0.50
Azathioprine	8 (2.8%)	1 (0.7%)	7 (4.7%)	0.069
Anti-TNF	2 (0.7%)	1 (0.7%)	1 (0.7%)	> 0.99
ICS	36 (13%)	21 (16%)	15 (10%)	0.17
Recurrence				
Yes	44 (56%)	17 (47%)	27 (64%)	0.13
No	34 (44%)	19 (53%)	15 (36%)	
Unknown	206	99	107	

Anti-TNF (anti-tumor necrosis alpha), B symptoms (fever, night sweats, and weight loss), ICS = inhaled corticosteroids, Scadding grade (0 = normal X-ray, 1 = bilateral hilar lymphadenopathy without parenchymal infiltrates, 2 = bilateral hilar lymphadenopathy without parenchymal infiltrates, 3 = pulmonary infiltrates without hilar lymphadenopathy, 4 = pulmonary fibrosis or lung conglomerate opacities)

*Total for each population

**Significance of the difference between Arab and Jewish per each variable

Bold signifies statistical significance

PFT results were collected from 73% of patients. Of these, 43% had impaired results: 36% exhibited a restrictive pattern (defined as TLC < 80% of predicted), 15% had an obstructive pattern (defined as forced expiratory volume in the first second (FEV1)/forced vital capacity (FVC) < 70% of predicted), and 3% had a mixed disorder. In addition, 15% had impaired FVC and/or FEV1 without a definitive obstructive or restrictive pattern. Notably, nearly all patients with impaired pulmonary function tests also had diffusion impairment (97%), defined as DLCO < 80% of predicted.

Laboratory blood test results showed no significant differences between the Arab and Jewish populations. Regarding chest radiographic disease extent, classified by the Scadding scale, 85% of patients presented with Scadding stages 1 and 2. The distribution of Scadding stages was as follows: 7% presented at stage 0, 44% at stage 1, 41% at stage 2, 3.2% at stage 3, and 4.6% at stage 4, with no significant differences observed between the Arab and Jewish populations [Table 2]. Most patients (67%) did not receive systemic treatment. Among those who did, corticosteroids were the first line, and 14% also received steroid-sparing therapy, most commonly methotrexate, which was prescribed significantly more frequently in the Jewish population. Follow-up data after the disease course were available for only a subset of patients, as at least 5 years of follow-up is required and the majority of our cohort did not meet this criterion. However, from the collected data of 78 patients, recurrence following treatment was observed in 56% of patients, higher in the Jewish population but without statistical significance [Table 2].

COMPARISON TO WORLD DATA

When comparing our data to global data presented in the ACCESS study [14], several observations arise [Table 3]. First, lung involvement is significantly less frequent in the Jewish population (95.1% in the ACCESS study vs. 83.9% in our Jewish cohort). Notably, the Arab population did not show a similar difference. Regarding joint involvement, the Israeli population (both Jewish and Arab) had a significantly higher rate of joint involvement (0.5% in the ACCESS study vs. 8.3% in our Israeli cohort). Eye and skin involvement appear to be significantly lower in the Israeli population as compared to global data, although the difference in skin involvement is significantly lower only in the Arab population.

Table 3. Comparison to world data (ACCESS Study)

	World data (ACCESS study) N=736	Total Israeli population N=300*	*P*-value	Jewish population n=149	*P*-value	Arab population n=135	*P*-value
Lungs	95.1%	87.3%	0.000	83.9%	0.000	91.9%	0.124
Cardiac	2.3%	4.3%	0.078	4%	0.230	4.4%	0.155
Joints	0.5%	8.3%	0.000	8.1%	0.000	8.9%	0.000
Eye	11.8%	4.7%	0.000	6.7%	0.069	3%	0.002
Renal	0.7%	1.7%	0.140	1.3%	0.405	2.2%	0.084
Hypercalcemia	3.8%	3.7%	0.916	6.7%	0.110	0%	0.021
Neurologic (CNS)	4.6%	2%	0.047	3.4%	0.493	0.7%	0.035
Liver/gastrointestinal	11.5%	8.7%	0.147	9.4%	0.447	8.2%	0.246
Skin	15.9%	8%	0.001	10.1%	0.069	4.4%	0.000
Sinus/URT	3%	1.7%	0.226	2%	0.512	1.5%	0.325
Bone marrow	3.9%	1.3%	0.030	2%	0.251	0.7%	0.061

*284 were included in our analysis
CNS = central nervous system, URT = upper respiratory tract

DISCUSSION

In this study, we reviewed and compared a population of 284 Jewish and Arab Israeli patients with sarcoidosis. Several findings emerged. The main findings of our study are as follows: age of disease presentation was significantly higher in the Jewish compared to the Arab population, EBUS was the most common modality of pathological diagnosis and use of steroid sparing agents was more frequent in the Jewish compared to the Arab population. In Israel, pulmonary involvement was similar, joint involvement was more frequent, and eye and skin involvement were less frequent compared to world data.

DEMOGRAPHY

We found a significantly higher mean age at diagnosis in the Israeli population, particularly among Jewish patients compared to Arab patients. While in the global consensus the peak age at diagnosis is in the fourth decade of life [14]. Our data suggest a later peak in the Israeli population: in the fifth decade among Arab patients and in the sixth decade among Jewish patients. This observation is supported by previous studies on the Israeli population [9,10]. The relatively earlier onset among Israeli Arab patients may be attributed to rural residence and potential occupational exposures. Regarding the Jewish population, one possible explanation is the bimodal nature of the disease, with a second peak occurring after age 50 years, as demonstrated in earlier studies [5]. In the Jewish Israeli population, the initial peak may be milder and may not necessarily lead patients to seek medical attention. Another plausible explanation involves unique genetic and environmental factors that remain to be fully elucidated. Regarding smoking history, although a trend toward higher rates was observed in the Arab population, the difference between Jewish and Arab groups was not statistically significant, despite smoking being more prevalent in the Arab population. This lack of significance may be explained by the proposed protective effect of cigarette smoking in sarcoidosis [15,16], although the matter is likely more complex and may be related to specific gene polymorphisms [17].

MODE OF DIAGNOSIS

EBUS was the most common diagnostic modality, with no significant difference between the Jewish and Arab populations, likely due to the high accessibility of medical services across Israel. However, more Jewish patients were clinically diagnosed based on disease presentation and compatible radiographic features without biopsy confirmation (24% vs. 11%, respectively, $P = 0.0042$). Whether this finding reflects a reluctance among older Jewish patients with sarcoidosis to undergo invasive procedures, or represents a different disease phenotype, remains to be determined.

PULMONARY FUNCTION TEST

Of the patients with documented pulmonary function test, 43% had impaired results, which is slightly higher than previous reports [18]. Among those with impaired PFT,

36% exhibited a restrictive pattern and 15% had an obstructive pattern, similar to previously described in the global population [14]. Contrary to previously observed differences in spirometry among different ethnic groups [19], no differences were found between Jewish and Arab patients in our study. Nearly all patients with impaired PFTs also had diffusion impairment; however, clinically significant diffusion impairment (defined as DLCO < 60% of predicted) [18] was observed in only 23% of patients.

DISEASE-SPECIFIC FEATURES

Authors of the largest study that reviewed the disease characteristic in the Arab population living in the Middle East found that overall, the clinical picture of patients with sarcoidosis in the Middle East appeared to be similar to that reported elsewhere in the world [20]. Yigla et al. [10] found that Jewish and Arabic patients had a similar proportion of thoracic involvement, but Jewish patients presented with more multi-organ involvement expressed by a higher prevalence of extra-pulmonary involvement (58.3% vs. 29.1%, respectively). Our study, however, did not show differences in the prevalence of multi-systemic disease extent between these two groups.

When reviewing the differences of disease extent in terms of organ involvement, lung involvement was not significantly different between the Jewish and Arabic population. When we performed a sub-analysis of the Jewish population, lung involvement was significantly more prominent in Ashkenazi compared to Sephardi Jews. Conversely, joint involvement was significantly more prevalent in the Sephardi group. No significant differences were observed in a similar sub-analysis of the Arab population between Christians and Muslims. Hypercalcemia was observed exclusively in the Jewish population in a minority of patients. Whether this observation truly reflects an ethnic derived difference is difficult to determine due to the low prevalence of hypercalcemia in sarcoidosis world-wide, which is 3.7% [14]. From our limited data regarding recurrence rate due to lack of sufficient years of follow up in most patients, 56% of the patients had a recurrence, a finding which was higher in the Jewish population but not statistically significant.

COMPARISON TO WORLD DATA

We also compared our results to the global data derived from the ACCESS study [8] and found several interesting observations. First, lung involvement was significantly less frequent in the Jewish population (95.1% in the ACCESS study vs. 83.9% in our Jewish cohort). Notably, the Arab population did not show a similar difference. Regarding joint involvement, the Israeli population (both Jewish and Arab) had a significantly higher rate of joint involvement (0.5% in the ACCESS study vs. 8.3% in our Israeli cohort). Eye and skin involvement were also significantly lower in the Israeli population as compared to global data, due to lower prevalence in the Arab population only. The difference in skin involvement might be partially explained by the inclusion of erythema nodosum as a skin manifestation in the ACCESS study.

The limitations of our study include its retrospective nature and reliance on medical records with some missing and incoherent documentation. The strength of our study lies in its size, which to date is the largest of its kind reviewing the Israeli population. In addition, it is unique in that it includes a comparison between several ethnic groups within the Israeli population as well as with global data on disease extent.

CONCLUSIONS

Sarcoidosis in the Israeli population is characterized by unique disease presentations and clinical manifestations across its distinct ethnic groups, and in comparison with global data. The underlying factors contributing to this diversity, whether genetic, occupational, or environmental, remain unclear and warrant further studies.

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References

1. Grunewald J, Grutters JC, Arkema EV, Saketkoo LA, Moller DR, Muller-Quernheim J. Sarcoidosis. *Nat Rev Dis Primers* 2019; 5 (1): 45.
2. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. *N Engl J Med* 2007; 357 (21): 2153-65.
3. Newman LS, Rose CS, Maier LA. Sarcoidosis. *N Engl J Med* 1997; 336 (17): 1224-34.
4. Hena KM. Sarcoidosis epidemiology: race matters. *Front Immunol* 2020; 11: 537382.
5. Costabel U, Hunninghake GW. ATS/ERS/WASOG statement on sarcoidosis. Sarcoidosis Statement Committee. American Thoracic Society. European Respiratory Society. World Association for Sarcoidosis and Other Granulomatous Disorders. *Eur Respir J* 1999; 14 (4): 735-7.

6. Gerke AK, Judson MA, Cozier YC, Culver DA, Koth LL. Disease burden and variability in sarcoidosis. *Ann Am Thorac Soc* 2017; 14 (Supplement 6): S421-S8.
7. Cozier YC. Assessing the worldwide epidemiology of sarcoidosis: challenges and future directions. *Eur Respir J* 2016; 48 (6): 1545-8.
8. Brito-Zeron P, Kostov B, Superville D, Baughman RP, Ramos-Casals M, Autoimmune Big Data Study G. Geoepidemiological big data approach to sarcoidosis: geographical and ethnic determinants. *Clin Exp Rheumatol* 2019; 37 (6): 1052-64.
9. Markevitz N, Epstein Shochet G, Levi Y, Israeli-Shani L, Shitrit D. Sarcoidosis in Israel: clinical outcome status, organ involvement, and long-term follow-up. *Lung* 2017; 195 (4): 419-24.
10. Yigla M, Badarna-Abu-Ria N, Goralnik L, Rubin AH, Weiler-Ravell D. Sarcoidosis in residents of northern Israel of Arabic and Jewish origin: a comparative study. *Respirology* 2006; 11 (5): 586-91.
11. Shohat T, Green MS, Davidson Y, Livne I, Tamir R, Garty BZ. Differences in the prevalence of asthma and current wheeze between Jews and Arabs: results from a national survey of schoolchildren in Israel. *Ann Allergy Asthma Immunol* 2002; 89 (4): 386-92.
12. Barak Levitt J, Barmatz S, Fisch-Gilad S, et al. A comparison of hidradenitis suppurativa characteristics among Israeli Arabs and Jews: analysis of two cohorts. *IMAJ* 2024; 26 (5): 283-8.
13. Alter R, Cohen A, Guigue PA, Meyer R, Levin G. Ethnic disparities in the incidence of gynecologic malignancies among Israeli women of Arab and Jewish ethnicity: a 10-year study (2010-2019). *Ther Adv Reprod Health* 2024; 18: 26334941231209496.
14. Baughman RP, Teirstein AS, Judson MA, et al. Clinical characteristics of patients in a case control study of sarcoidosis. *Am J Respir Crit Care Med* 2001; 164 (10 Pt 1): 1885-9.
15. Newman LS, Rose CS, Bresnitz EA, et al. A case control etiologic study of sarcoidosis: environmental and occupational risk factors. *Am J Respir Crit Care Med* 2004; 170 (12): 1324-30.
16. Dehara M, Nguyen NV, Arkema EV. Smoking and the risk of sarcoidosis: a systematic review and meta-analysis. *Respir Med* 2025; 241: 108089.
17. Rivera NV, Patasova K, Kullberg S, et al. A gene-environment interaction between smoking and gene polymorphisms provides a high risk of two subgroups of sarcoidosis. *Sci Rep* 2019; 9 (1): 18633.
18. Yao Q, Ji Q, Zhou Y. Pulmonary function in pulmonary sarcoidosis. *J Clin Med* 2023; 12 (21): 6701.
19. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999; 159 (1): 179-87.
20. Jayakrishnan B, Al-Busaidi N, Al-Mubaihsi S, Al-Rawas OA. Sarcoidosis in the Middle East. *Ann Thorac Med* 2019; 14 (2): 106-15.

You can preach a better sermon with your life than with your lips.

Oliver Goldsmith (1730–1774), Anglo-Irish poet, novelist, playwright, and hack writer

Capsule

Autoimmune response to C9orf72 protein in amyotrophic lateral sclerosis

Autoimmune responses are thought to have a key role in amyotrophic lateral sclerosis (ALS) pathology, and it is hypothesized that T cells contribute to the rapid loss of neurons during disease progression. **Michaelis** and colleagues showed that ALS is associated with recognition of the C9orf72 antigen. The authors mapped the specific epitopes that are recognized. They showed that these responses are mediated by $CD4^+$ T cells that preferentially release IL-5 and IL-10, and that IL-10-mediated T cell responses are significantly greater in donors who have a longer predicted survival time. These results reinforce the previous hypothesis that neuroinflammation has an important role in ALS disease progression, possibly because of a disrupted balance of inflammatory and counter-inflammatory T cell responses. These findings highlight the potential of therapeutic strategies aimed at enhancing regulatory T cells and identify a key target for antigen-specific T cell responses that could enable precision therapeutics in ALS.

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Capsule

Redesigning antibody therapeutics

Autoimmune diseases can be treated by intravenous immunoglobulin (IVIG), a therapeutic that requires substantial quantities of antibodies to be collected from large numbers of healthy human donors. Based on one proposed mechanism of action for IVIG, **Jones** and colleagues produced an antibody tail fragment known as the Fc region and modified it so that it inhibited pathology in mouse modals of autoimmunity with a lower dose than IVIG. This engineered Fc protein was modified by sialylation and contained mutations that increased its interaction with a type I receptor known as FcγRIIB. The interaction between FcγRIIB and another receptor, DC-SIGN, promoted the binding of isolated Fc fragments and antibodies to cells.

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