The Association of Vasculitis Incidence and Seasonality: A Retrospective National Study

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ABSTRACT The potential influence of seasonal variations on vasculitis is unclear. Emerging evidence has suggested that seasonal factors may play a role in the onset of vasculitis. We extracted data from the electronic medical records at Clalit Health Services (CHS), Israel's largest health maintenance organization. We identified patients older than 18 years of age with new onset of giant cell arteritis (GCA), ANCA-associated vasculitis, immunoglobulin A (IgA) vasculitis, and Behçet's disease from 2007 to 2021. We constructed a time series of new vasculitis cases per month and explored the potential impact of seasonality on the disease onset. Our cohort included 4847 patients, including 2445 with GCA, 749 with ANCA-associated vasculitis (AAV), 547 with IgA vasculitis, and 1106 with Behçet's disease. We observed a decreased risk of GCA in September (relative risk [RR] 0.84, [95% confidence interval] 95%CI 0.72–0.98) and a significant reduction in AAV incidence in August (RR 0.68, 95%CI 0.48–0.96). For IgA vasculitis, an elevated risk was noted in February (RR 1.58, 95%CI 1.02–2.45), while Behçet's disease showed an increased risk in January (RR 1.25, 95%CI 1.02–1.55). No association was found between any specific season and the onset of vasculitis for any of the studied conditions. Our study results indicate that the onset of vasculitis conditions may be influenced by environmental factors associated with seasonality.

IMAJ 2025; 27: 464–470

KEY WORDS: ANCA-associated vasculitis, giant cell arteritis (GCA), immunoglobulin A (IgA) vasculitis, vasculitis

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Vasculitis, a heterogeneous group of disorders characterized by inflammation of blood vessels, poses significant challenges in diagnosis and management due to its varied clinical presentations and unpredictable disease course [1]. While genetic predisposition, environmental triggers, and dysregulated immune responses have been implicated in its pathogenesis [2,3], the potential influence of seasonal variations on vasculitis remains a topic of considerable interest and debate.

Emerging evidence has suggested that seasonal factors may play a role in the onset and exacerbation of vasculitis. For example, viral infections, possible triggers for vasculitis, often exhibit seasonal incidence patterns, with peaks occurring during specific times of the year, such as with Henoch-Schönleinpurpura and seasonal viruses [4]. Moreover, fluctuations in environmental allergens and ultraviolet radiation exposure have been implicated in the pathogenesis of autoimmune diseases such as systemic lupus erythematosus [5].

Despite these observations, comprehensive studies examining the impact of seasonality on vasculitis are still lacking. Existing literature consists of anecdotal reports, small-scale observational studies, and retrospective analyses with conflicting findings [6,7]. Therefore, there is a critical need for well-designed prospective studies to elucidate the potential association between seasonality and vasculitis.

We investigated the influence of seasonality on vasculitis through a comprehensive observational analysis by leveraging a large cohort of patients with vasculitic diseases to examine temporal trends in disease incidence.

METHODS

POPULATION

Data were extracted from electronic patients records at Clalit Health Services (CHS), Israel's largest health maintenance organization, which insures 52% of the Israeli population (approximately five million people). According to the Israel Central Bureau of Statistics, the CHS population can be considered as a reflection of the overall Israeli population [8]. Data were extracted using the Clalit Research

Data sharing platform powered by MDClone (http://www.mdclone.com). The electronic medical records are available and updated in real-time at the patient level, including patient demographics, medical history, and community and hospital diagnoses. In addition, data on individual medication purchases in CHS pharmacies are also available. The study was approved by Soroka Medical Center institutional ethics committee (SOR21-0194).

THE INCIDENCE OF IGA VASCULITIS AND ANCA-ASSOCIATED VASCULITIS SHOWED SIGNIFICANT SEASONAL VARIATIONS, WITH IGA VASCULITIS PEAKING IN FEBRUARY AND ANCA-ASSOCIATED VASCULITIS DEMONSTRATING A HIGHER RISK DURING THE WINTER AND SPRING.

CASE IDENTIFICATION

We identified CHS patients diagnosed with vasculitis according to International Classification of Diseases (ICD-9) codes for giant cell arteritis (GCA) (446.5), ANCA-associated vasculitis (AAV) (446, 447.6), immunoglobulin A (IgA) vasculitis (287.0), and Behçet's disease (BD) (136.1). AAV included granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, microscopic polyangiitis, and polyarteritis nodosa (PAN). As the ICD-9 codes for microscopic polyangiitis and polyarteritis nodosa are identical, distinguishing between these conditions was not feasible. We included all patients older than 18 years of age who received the diagnoses from 2007 to 2021 and we identified a record of medications pertinent to vasculitis treatment purchased in the year following the diagnosis. Specifically, we considered the following drugs: glucocorticoids (of any type), disease-modifying antirheumatic drugs (e.g., methotrexate, azathioprine, mycophenolate), biological therapies, and cyclophosphamide. To ensure that cases with previous diagnoses of vasculitis conditions were not included in the final analysis, we used a run-in period (disease-free observation period) of those diagnosed with vasculitis between 2002 and 2006 [9].

Table 1. General characteristics of individuals in Israel diagnosed with vasculitides between 2007 and 2021

	GCA (n=2445)	AAV (N=749)	IgA vasculitis (n=547)	Behçet's disease (n=1106)
Age at diagnosis, years, mean ± SD (n)	63.1 ± 7.9	45.3 ± 14.0	48.5 ± 16.6	34.1 ± 12.4
Females, n/N (%)	1610 (65.8)	439 (58.6)	306 (55.9)	623 (56.3)
Ethnicity				
Jewish, n (%)	2171 (88.8)	618 (82.5)	423 (77.3)	684 (61.8)
Muslim, n (%)	274 (11.2)	131 (17.5)	124 (22.7)	422 (38.2)
SES quintiles, median (IQR)	3.0 (3.0–4.0)	3.0 (2.0–4.0)	3.0 (2.0–4.0)	3.0 (2.0–4.0)
Follow-up from diagnosis, years, median (IQR)	6.0 (3.0–9.0)	6.0 (2.0–9.0)	5.0 (1.0–9.0)	8.0 (4.0–12.0)
Co-morbidities				
Diabetes, n (%)	925 (37.8)	176 (23.5)	205 (37.5)	144 (13.0)
Chronic kidney disease, n (%)	477 (19.5)	157 (21.0)	163 (29.8)	30 (2.7)
Coronary artery disease, n (%)	264 (10.8)	57 (7.6)	78 (14.3)	31 (2.8)
Stroke, n (%)	769 (31.5)	100 (13.4)	119 (21.8)	87 (7.9)
Malignancy, n (%)	390 (16.0)	92 (12.3)	81 (14.8)	53 (4.8)
Charlson Comorbidity Index score, median (IQR)	6.0 (5.0–8.0)	3.0 (2.0–5.0)	4.0 (2.0–7.0)	2.0 (1.0–3.0)
Never smoked, n (%)	1766 (72.2)	467 (62.3)	343 (62.7)	749 (67.7)
Treatments for vasculitides in the year of diagnosis				
Prednisone, n (%)	2371 (97.0)	719 (96.0)	525 (96.0)	918 (83.0)
DMARDs	722 (29.5)	417 (55.7)	175 (32.0)	774 (70.0)
Rituximab or cyclophosphamide, n (%)	74 (3.0)	216 (28.8)	32 (5.9)	30 (2.7)
Other biologics, n (%)	184 (7.5)	32 (4.3)	19 (3.5)	145 (13.1)
Five-year mortality, n (%)	529 (21.6)	97 (13.0)	161 (29.4)	33 (3.0)

Demographics were extracted from the year of diagnosis, and co-morbidities were extracted from the last year of follow-up

AAV = anti-neutrophil cytoplasmic autoantibody-associated vasculitis, GCA = giant cell arteritis, DMARDs = disease-modifying antirheumatic drugs, IQR = interquartile range, SES = socioeconomic status

Figure 1. Monthly new cases between 2007 and 2021

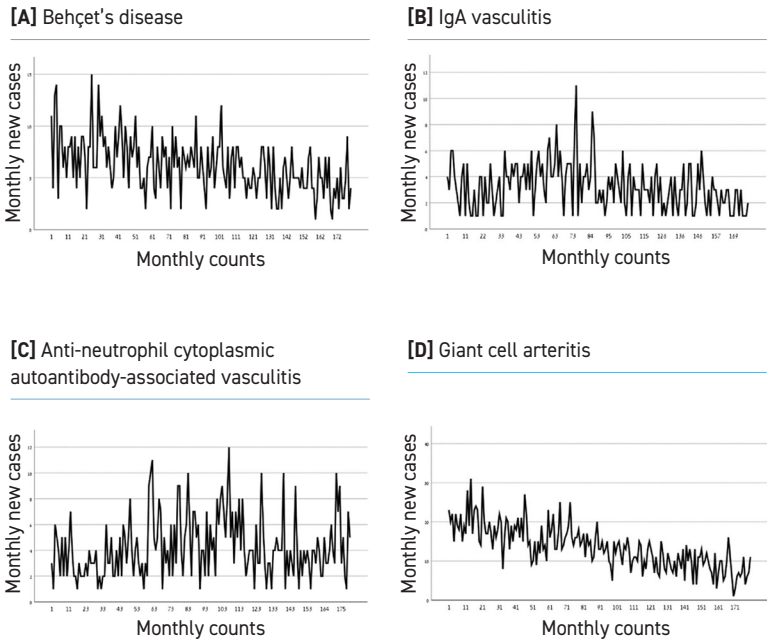
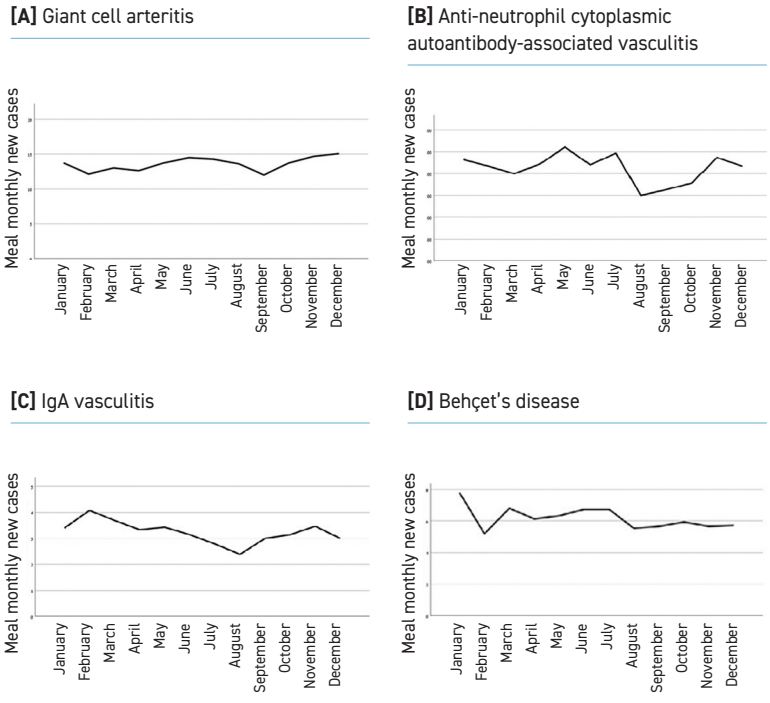


Figure 2. Mean monthly new cases between 2007 and 2021



SEASONALITY

We constructed a time series of new cases of vasculitis per month and have explored the possible impact of seasonality on the onset of the disease. Seasons in Israel were defined according to definitions established by Alpert and co-authors: winter (7 December–30 March), spring (31 March–30 May), summer (31 May–22September), and autumn (23 September–6 December) [10].

STATISTICAL ANALYSIS

The data were described using percentages, means, standard deviations, medians, and interquartile ranges. We calculated the average number of incident cases of vasculitides per calendar month between 2007–2021. We restricted the analysis to ages older than 50 years for GCA and used a threshold of older than 18 years for all the other conditions.

We applied Poisson regression modeling to calculate the relative risk (RR) and the 95% confidence interval (95%CI) of the estimated monthly incidence of each vasculitis condition during the study period using a month as a binary indicator and the annual estimate of the population at risk (e.g., the general population older than 50 years for GCA) as an offset. Each month was tested in a separate model. Identical methods were used to estimate the contribution of the season. We did not adjust for multiple comparisons in our analysis.

We examined the annual circle of the monthly seasonality of new vasculitis cases using sine and cosine harmonic functions defined as:

$\text{Sin} = \sin(2 * \pi * 1/12 * t)$ $\cos = \cos(2 * \pi * 1/12 * t)$, where t = the consecutive number of months.

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 28 (SPSS, IBM Corp, Armonk, NY, USA).

RESULTS

The demographic and clinical characteristics of 4847 individuals diagnosed with various vasculitides in Israel between 2007 and 2021 are shown in Table 1. The mean age at diagnosis varied across diseases, with GCA patients being the oldest (63.1 ± 7.9 years) and Behçet's patients the youngest (34.1 ± 12.4 years). A higher proportion of females was observed in all groups, especially in GCA (65.8%). Jews represented the majority of the patients, although Muslims had higher representation in Behçet's disease (38.2%) compared to other vasculitides. We also found that socioeconomic status was sim-

ilar across groups, with a median SES of 3 (IQR 2–4). Co-morbidities, particularly diabetes (13.0–37.8%) and chronic kidney disease (2.7–29.8%), were frequent. Stroke prevalence was highest in GCA (31.5%), while malignancy rates were notable in GCA (16.0%) and IgA vasculitis (14.8%). Prednisone was the most commonly used treatment across all vasculitides, particularly in GCA (97.0%), while the use of disease-modifying antirheumatic drugs (DMARDs) was higher in Behçet's (70.0%) and AAV (55.7%). Rituximab or cyclophosphamide was more frequently administered to AAV patients (28.8%). Five-year mortality rates varied significantly, with IgA vasculitis the highest (29.4%) and Behçet's disease the lowest (3.0%).

ENVIRONMENTAL AND SEASONAL FACTORS, SUCH AS INFECTIONS AND CLIMATIC CHANGES, MAY INFLUENCE THE ONSET OF CERTAIN VASCULITIDES, HIGHLIGHTING AVENUES FOR PREVENTIVE STRATEGIES AND TAILORED PATIENT MANAGEMENT.

The analysis of associations between the onset of vasculitis and temporal factors, such as months and seasons, is shown in Table 2. For GCA, the relative risk showed a trend toward elevated risk in January (RR 1.10, 95%CI 0.94–1.28) and June (RR 1.08, 95%CI 0.94–1.23), while a decreased risk was observed in September (RR 0.84, 95%CI 0.72–0.98). AAV demonstrated a trend toward increased relative risk in May (RR 1.24, 95%CI 0.93–1.64) and November (RR 1.14, 95%CI 0.85–1.54), although the most significant decrease occurred in August (RR 0.68, 95%CI 0.48–0.96). For IgA vasculitis, a heightened risk was seen in February (RR 1.58, 95%CI 1.02–2.45), whereas Behçet's disease exhibited an increased risk in January (RR 1.25, 95%CI 1.02–1.55). Across seasons, winter and spring were generally associated with a trend toward increased relative risks across most vasculitides, but these associations did not reach statistical significance.

Figure 1 presents the monthly incidence of four distinct vasculitic diseases from 2007 to 2021:highlighting the temporal fluctuations in the diagnoses of these disorders across the period. Figure 2 illustrates the mean monthly in-

Table 2. Associations of the months and seasons with the new onset of vasculitis by type

	GCA		AAV		IgA vasculitis		Behçet's disease	
Period	**RR**	**95%CI**	**RR**	**95%CI**	**RR**	**95%CI**	**RR**	**95%CI**
Month								
January	1.10	0.94–1.28	1.11	0.81–1.51	1.40	0.88–2.22	1.25	1.02–1.55
February	0.92	0.79–1.08	1.01	0.74–1.37	1.58	1.02–2.45	0.79	0.62–1.01
March	0.99	0.85–1.15	0.97	0.72–1.32	1.42	0.91–2.20	1.09	0.88–1.34
April	0.94	0.81–1.10	1.03	0.76–1.40	1.30	0.84–1.99	0.97	0.78–1.21
May	1.03	0.89–1.18	1.24	0.93–1.64	1.31	0.86–2.00	1.02	0.82–1.25
June	1.08	0.94–1.23	1.04	0.77–1.39	1.19	0.78–1.82	1.10	0.89–1.34
July	1.05	0.91–1.20	1.18	0.89–1.55	1.00	0.65–1.54	1.10	0.90–1.35
August	0.98	0.85–1.13	0.68	0.48–0.96	0.86	0.55–1.36	0.89	0.71–1.12
September	0.84	0.72–0.98	0.75	0.53–1.05	1.06	0.70–1.60	0.92	0.74–1.15
October	0.96	0.83–1.12	0.83	0.59–1.16	1.07	0.71–1.59	0.98	0.78–1.22
November	1.03	0.89–1.19	1.14	0.85–1.54	1.17	0.80–1.73	0.93	0.74–1.17
December	1.06	0.91–1.23	1.03	0.75–1.41	0.90	0.65–1.24	0.95	0.75–1.20
Season								
Summer	0.98	0.90–1.07	0.89	0.74–1.07	0.83	0.70–1.00	1.02	0.89–1.15
Autumn	0.95	0.84–1.07	1.00	0.80–1.24	1.08	0.8–1.35	0.95	0.82–1.11
Winter	1.02	0.93–1.18	1.07	0.89–1.28	1.16	0.98–1.38	1.02	0.89–1.16
Spring	1.02	0.92–1.14	1.14	0.92–1.40	1.17	0.95–1.43	1.04	0.89–1.21

The models were adjusted for month and population size
95%CI = 95% confidence interval, AAV = anti-neutrophil cytoplasmic autoantibody-associated vasculitis, GCA = giant cell arteritis, RR = relative risk

cidence of these vasculitis syndromes. The yearly cyclical pattern was statistically significant for ANCA-associated vasculitis ($P = 0.03$) and IgA vasculitis ($P = 0.01$), suggesting seasonal or periodic variations in these conditions.

DISCUSSION

Seasonality, characterized by cyclic changes in environmental factors such as temperature, humidity, and daylight duration, has been implicated in the incidence and severity of various autoimmune and inflammatory diseases, including rheumatoid arthritis and systemic lupus erythematosus [11]. However, the relationship between seasonality and vasculitis remains underexplored, necessitating more in-depth investigation.

Our cohort represented a real-life registry on a nationwide scale validated in previous studies. We further enhanced the validity of our cohort by including only patients diagnosed with vasculitis and issued a relevant treatment during the year of their diagnosis. The findings reveal that while certain vasculitides exhibit potential seasonal tendencies, others do not. Specifically, some months demonstrated statistical significance regarding the incidence of vasculitis, suggesting a possible environmental influence. These findings are consistent with prior research indicating that external environmental factors may play a role in the onset of autoimmune diseases [12]. However, the variations between the types of vasculitis highlight the complexity of these interactions.

GIANT CELL ARTERITIS AND BEHÇET'S DISEASE SHOWED WEAKER OR NO SIGNIFICANT ASSOCIATIONS WITH SEASONALITY, SUGGESTING DISTINCT PATHOPHYSIOLOGICAL PATHWAYS COMPARED TO OTHER VASCULITIDES.

In GCA, our findings align with the results of a comprehensive meta-analysis by Hysa et al. [7], which found no clear seasonal pattern in GCA. However, there was a trend, although non-significant statistically, toward an increased risk of disease onset during the warmer months. In contrast, our research identified September as a statistically significant lower risk of GCA onset, with a general trend toward lower incidence during the autumn, when temperatures are cooler. The results of our study add to the trend from a previous study that included 174 biopsies, which showed an increased tendency for the onset of biopsy-proven GCA that peaked in May through July [13]. A recent large study of biopsy-proven GCA patients observed a similar seasonal variation [14].

A possible explanation may involve increased sunlight exposure in hot weather, which has been hypothesized to trigger immunological reactions. Wing and colleagues [15] demonstrated that auroral electrojet and geomagnetic activity may explain the periodic incidence in GCA. Furthermore, vascular disruption caused by heat might induce the formation of new antigenic determinants, provoking autoimmune responses [16].

In contrast, AAV demonstrated a more apparent seasonal pattern, with a higher incidence in the winter and spring. This finding corresponds with several previous studies that also found an increased risk during colder months [17,18]. However, other research has produced mixed results, with some studies observing a predominantly winter-based seasonal tendency [19], while others report no such correlation [20]. Zhao et al. [6] proposed that different triggers, such as respiratory infections in the winter [21], low vitamin D levels [22], and sun exposure or pollutants in the summer, might contribute to the seasonal variability in AAV onset. A recent large study by Yoshida et al. [23] showed that the onset of AAV was less likely in the autumn and that seasonality was significant in patients with MPO-ANCA but not in PR3-ANCA patients.

These multifactorial influences suggest that environmental triggers may vary significantly across seasons, further complicating the understanding of seasonal effects on AAV.

Our findings regarding IgA vasculitis corroborate previous studies, showing an increased incidence during the winter [24]. This seasonal trend has been attributed to viral infections such as respiratory syncytial virus and influenza, both more prevalent in colder months. Vitamin D deficiency has been increasingly recognized as a potential contributor to the pathogenesis of various autoimmune conditions, including IgA vasculitis [25].

Our findings reveal a higher 5-year mortality rate in IgA vasculitis patients than in other vasculitides. This conclusion aligns with studies such as Nossent and colleagues [26], which highlighted increased mortality in adult-onset IgA vasculitis, driven by severe infections and co-morbidities like renal failure. The elevated burden of cardiovascular, pulmonary, and renal conditions before diagnosis likely contributes to these outcomes.

Last, we did not identify a significant seasonal trend in the onset of Behçet's disease. The literature on seasonality in Behçet's disease is sparse, with only one study reporting a higher incidence of intestinal manifestations of the disease in the spring and summer [27]. In contrast, another study has shown no correlation between Bechet's disease symptoms and seasonality except for arthralgia [28]. Giv-

en this limited data, further research is needed to elucidate the potential environmental or seasonal factors influencing Behçet's disease. Such factors may differ from those identified in other vasculitides and could involve more localized or disease-specific environmental triggers.

Air pollution is increasingly recognized as a significant factor influencing the development and progression of rheumatic diseases. Pollutants such as fine particulate matter and nitrogen dioxide (NO_2) have been linked to an increased risk of systemic autoimmune diseases, likely through mechanisms including oxidative stress, immune dysregulation, and epigenetic changes. In addition, climate change exacerbates air pollution, amplifying these effects [29].

Our study has several limitations, which provide opportunities for future research. First, as a retrospective study, causality between the incidence of vasculitis and seasonality cannot be definitively established. Second, our cohort was based on ICD-9 codes rather than European Alliance of Associations for Rheumatology/American College of Rheumatology classifications for certain vasculitis conditions. However, in Israel, these diagnoses are assigned exclusively by rheumatologists, and the CHS cohort for autoimmune rheumatic diseases has been validated in previous study [30]. To further enhance validity, we included only patients who received relevant treatment for vasculitis within the year following their diagnosis.

In addition, while we examined seasonality with vasculitis onset, our study did not incorporate specific environmental factors such as temperature, air pollution, humidity, or daylight duration, which could influence the observed seasonal trends. Future studies integrating these data may help uncover potential mechanisms driving these associations.

Last, we used the timing of diagnosis as a proxy for disease onset. While this approach provided valuable insights, a delay often exists between the initial symptoms of vasculitis and its diagnosis due to the disease's evolving and sometimes ambiguous presentation. This limitation may obscure the precise timing of disease onset. Nevertheless, our study offers a robust analysis of diagnosis patterns, laying a strong foundation for future prospective studies that could better capture symptom onset and refine the temporal associations observed in this research.

CONCLUSIONS

Our study highlights a possible relationship between seasonality and vasculitis. While some forms of vasculitis, such as AAV and IgA vasculitis, demonstrate a more pronounced seasonal pattern, others, like GCA and Behçet's disease, show either weak or no clear associations. These findings have suggested that environmental factors, including infections, ambient temperature, and meteorological fluctuations, may play varying roles in the pathogenesis of different types of vasculitis. Further research is essential to clarify these relationships and identify the underlying mechanisms that could inform the timing and targeting of preventive strategies.

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Capsule

Structure of influenza RNP complex

Influenza viruses package their RNA genome with multiple nucleoproteins, and a ribonucleoprotein (RNP) complex containing a polymerase that drives viral genome transcription and replication, making it a promising drug target. Using advanced cryo-electron microscopy methods, **Peng** et al. revealed how RNA and nucleoproteins organize within the RNP complex and how the polymerase functions in this setup. They also identified compounds that interfere with interactions, thereby disrupting RNP function. These findings shed new light on how influenza viruses replicate and also paves the way for antiviral development.

Science 2025; 388: 721
Eitan Israeli

Capsule

Microglial mechanisms drive amyloid-β clearance in immunized patients with Alzheimer's disease

Alzheimer's disease (AD) therapies utilizing amyloid-β (Aβ) immunization have shown potential in clinical trials. Yet, the mechanisms driving Aβ clearance in the immunized AD brain remain unclear. **Olst** et al. used spatial transcriptomics to explore the effects of both active and passive Aβ immunization in the AD brain. They compared actively immunized patients with AD with nonimmunized patients with AD and neurologically healthy controls, identifying distinct microglial states associated with Aβ clearance. Using high-resolution spatial transcriptomics alongside single-cell RNA sequencing, the authors delved deeper into the transcriptional pathways involved in Aβ removal after lecanemab treatment. They uncovered spatially distinct microglial responses that vary by brain region. The analysis revealed upregulation of the triggering receptor expressed on myeloid cells 2 (*TREM2)* and apolipoprotein E (*APOE*) in microglia across immunization approaches, which correlated positively with antibody responses and Aβ removal. Furthermore, they showed that complement signaling in brain myeloid cells contributes to Aβ clearance after immunization. These findings provide new insights into the transcriptional mechanisms orchestrating Aβ removal and shed light on the role of microglia in immune-mediated Aβ clearance. This research uncovers potential molecular targets that could enhance Aβ-targeted immunotherapies, offering new avenues for developing more effective therapeutic strategies to combat AD.

Nature Med 2025; 31: 1604
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