MONOCYTE SUBSETS IN RELAPSING REMITTING MULTIPLE SCLEROSIS EGYPTIAN PATIENTS

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ABSTRACT

Background: *Although many types of immune cells are involved in multiple sclerosis (MS) progression, activated monocytes are believed to be one of the first to arrive at the brain and initiate inflammation. However, little is known about how the different monocyte subsets (classical, intermediate and non-classical) are involved in MS.*

Ain of the work: *The current study aims to investigate the presence of different subsets of monocytes in relapsing-remitting MS (RRMS) Egyptian patients and their correlation with disease activity.*

Patients and Methods: *This study included 44 RRMS patients (22 patients in relapse, 22 patients in remission), diagnosed according to the 2017 MacDonalds criteria, and 44 age-and sex-matched healthy controls. Full personal and medical histories were taken from the patients and Expanded Disability Status Scale (EDSS) was done to assess patients' disability. Characterization of monocyte subsets was done by flowcytometry for all participants.*

Results: *The percentage of classical, intermediate, and non-classical monocyte subsets showed a statistically significant increase in MS patients than controls with p values (0.029, 0.049, 0.043) respectively. No statistically significant difference in the frequency of the classical and intermediate monocyte subsets with any of the clinical parameters. However, patients with evidence of activity in MRI have a significantly high frequency of non-classical monocytes with p value (0.002). No statistically significant difference in the frequency of the non-classical monocyte subset with the other clinical parameters.*

Conclusion: *In MS relapse and remission, the three monocyte subsets (classical, intermediate & non-classical) increase significantly. This increase denotes the vital role of monocytes in disease pathology, as they might be related to disease activity, especially the non-classical monocyte subset. This finding makes monocytes a promising therapeutic target and a possible diagnostic tool for MS.*

Keywords: *Multiple sclerosis, Monocyte subsets*

INTRODUCTION:

Multiple sclerosis (MS) is a chronic autoimmune-mediated demyelinating disease of the central nervous system (CNS), usually associated with varying degrees of progressive disability. According to their clinical course, MS patients are categorized into four major subtypes; clinically isolated syndrome (CIS); an initial presentation of MS, relapsing-remitting MS (RRMS); the

most common type of MS, primary progressive MS (PPMS); clinically progressive disease without any recovery, and secondary progressive MS (SPMS); which usually develops after years of relapsing-remitting disease[1]. Early diagnosis of MS is necessary, and investigations such as MRI, blood and cerebrospinal fluid (CSF) analysis may aid in MS patients' evaluation[2].

Monocytes, macrophages and microglia have a central role in the CNS inflammation of MS mediating both pro- and anti-inflammatory responses [3]. Macrophages differentiate from circulating blood monocytes that mainly enter the CNS as part of an acute inflammatory response and contribute to disease progression and demyelinating activity. Depending on environmental stimuli, monocytes-macrophages undergo different phenotypic polarization, defined by surface receptor expression, effects or functions, cytokine and chemokine production [4]. At least three distinct monocyte subsets exist in the blood. Surface expression of CD14 and CD16 are used to distinguish classical ($CD14^{++}CD16^{-}$), intermediate ($CD14^{++}CD16^{+}$), and nonclassical ($CD14^{+}CD16^{++}$) monocyte subsets [5].

AIM OF THE WORK:

In this context, the current study aimed to investigate the presence of different monocyte subsets in RRMS Egyptian patients and their correlation with disease activity.

PATIENTS AND METHOD:

Subjects:

The present study included 44 patients with RRMS diagnosed according to the 2017 MacDonalds criteria [6]. They were selected from the outpatient clinic of the Neurology Department at Ain Shams University Hospital during the period (October 2020 - March 2021). They were divided into 22 in relapse and 22 in remission. Forty-four age- and sex-matched controls were also included.

Patients with other neurological diseases, chronic inflammatory diseases, tumors or suffer from severe obesity (Body Mass Index > 40 kg/m^2) were excluded from the study.

All patients and controls were subjected to the following:

- Full personal history taking including age, family history, occupation, and drug history.
- Full medical history taking, including MRI findings and oligoclonal bands in CSF.
- Neurological examination by EDSS assessment.
- Analysis of monocyte subsets by flow cytometry using CD14 and CD16 monoclonal antibodies.

Sample Collection and Storage:

From each participant, 2.5 ml of venous blood was withdrawn under complete aseptic conditions on a disodium ethylene diamine tetra acetic (EDTA) vacutainer tube. The collected samples were used in the flow cytometric analysis for the studied groups. Samples were processed within 2-3 hours of collection.

Ethical Consideration:

This research was approved by Ethical Research committee, faculty of Medicine, Ain Shams university, Date: 4/10/2020, No. FMASU: MS 514/2020.

Flow Cytometric Analysis of the Monocyte Subsets:

Reagents:

- Monoclonal antibodies:

  1- Fluorescein isocyanate (FITC) conjugated CD 16 (Beckman coulter, France) lot number: 200109.

2- Phycoerythrin (PE) conjugated CD 14 (Beckman coulter, France) lot number: 200080.

- Lysing solution: The lysing solution was prepared as follows: 89.2g NH4Cl, 8.4g NaHCO3, and 3.7g Disodium EDTA in 1 liter of distilled water at pH 7.2.

Steps:

Fifty µL of the specimen were pipetted in tubes labelled with the patient's name and the relevant monoclonal antibody. Five µL of fluorochrome-conjugated monoclonal antibodies were then added (CD14 PE and CD16 FITC). Then the tubes were incubated in the dark at room temperature for 15 minutes. Then 1 ml of lysing solution was added and left in the dark at room temperature for 10 minutes till complete RBCs lysis and the suspension became clear. Sample acquisition was done using Navios Flow cytometry (Beckman coulter, USA). The cells were selected based on Forward and side scattering intensity (FS-INT and SS-INT) to gate monocytes among other leucocytes (figure 1). Finally, monocytes, gated based on cell size and complexity, were plotted in a CD14 versus CD16 graph in order to characterize all three monocyte subpopulations: classical monocytes ($CD14^{+}CD16^{-}$), intermediate monocytes ($CD14^{+}CD16^{+}$) and non-classical monocytes ($CD14^{-}CD16^{+}$).

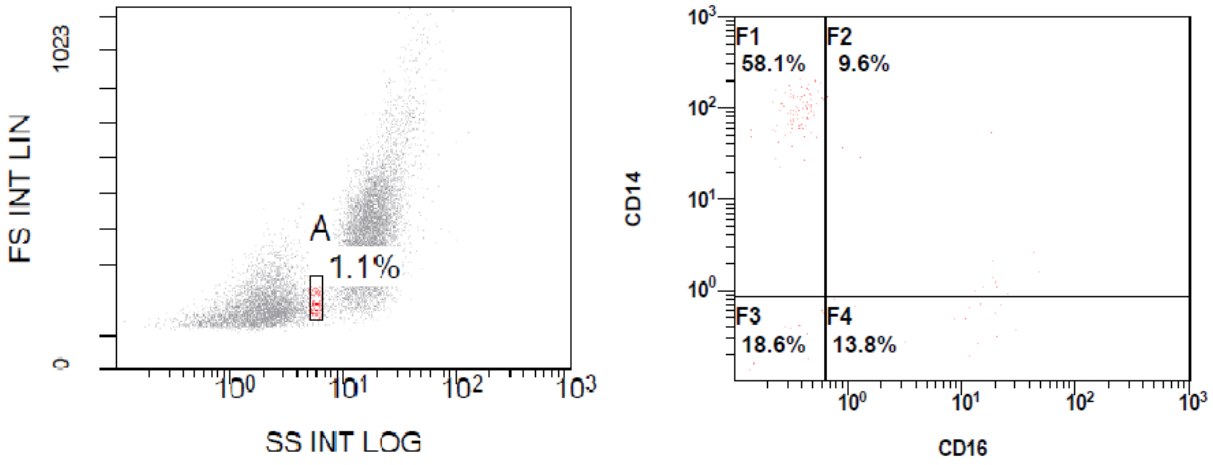

Figure (1): Gating strategy of monocytes subsets.

Statistical Methods:

Data were collected, revised, coded and entered into the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative parametric data were presented as mean, standard deviations and ranges, while nonparametric data were presented as median and inter-quartile range (IQR). Qualitative variables were presented as numbers and percentages. The comparison between groups regarding qualitative data was made using the Chi-square test. The comparison between two groups regarding quantitative parametric data was created using the independent t-test, while in nonparametric distribution the One-Way ANOVA test was used. The correlation of quantitative nonparametric data was done using the Spearman correlation coefficient. The confidence interval was set to 95%, and the margin of error accepted was set to 5%. P-value > 0.05 is non-significant (NS). While < 0.05 is significant (S) and < 0.01is highly significant(H) .

RESULTS:

Clinical data of the patients (n=44) regarding personal history and medical history are shown in in **table (1).**

Table (1): Description of MS patients' clinical data

			n., (%)
Family history	Negative		39 (88.6%)
	Positive		4 (9.1%)
	NA		1 (2.3%)
Drug administration	Negative		9 (20.5%)
	Positive		34 (77.3%)
	NA		1 (2.3%)
Current drug	Didn't start yet		9 (20.5%)
	Interferon beta	Rebif	8 (18.2%)
		Avonex	9 (20.5%)
		Betaferon	2 (4.5%)
	Dimethylfumarate		4 (9%)
	Fingolimod		10 (22.7%)
	Ocrelizumab		2 (4.5%)
EDSS*	Mean±SD		2.74 ± 1.34
	Range		1 – 7.5
MRI findings (evidence of activity)	Not done		8 (18.2%)
	No evidence of activity		19 (43.2%)
	Evidence of activity		3 (6.8%)
CSF – OCB	Not done		3 (6.8%)
	Positive		36 (81.8%)
Duration of the disease (years)	Median (IQR)		4.5 (3 – 6)
	Range		0.25 – 14
Number of activity (during last year)	Median (IQR)		1 (0.5 – 1)
	Range		0 – 2

*EDSS: Expanded disability status scale

The percentage of classical, intermediate, and non-classical monocyte subsets showed statistically significant differences between MS patients and controls, being statistically significantly higher in MS patients than controls as seen in **table 2**.

Table (2): Comparison between control group and patients regarding their classical, intermediate, and non-classical monocyte subset percentage

		Control group	**Patients group**	**Test value**	**P-value**	**Sig.**
		No.= 44	**No.= 44**			
Classical monocytes	Mean±SD	55.80 ± 11.02	61.88 ± 14.39	-2.227•	0.029	S
	Range	22.7 – 72.1	9.8 – 81.5			
Intermediate monocytes	Mean±SD	9.17 ± 6.36	11.98 ± 6.86	-1.993•	0.049	S
	Range	2 – 23.2	0.8 – 35.5			
Non classical	Mean±SD	11.44 ± 5.56	13.95 ± 5.88	-2.053•	0.043	S
	Range	2.4 – 30.4	0 – 38.5			

P-value > 0.05: Nonsignificant; p-value < 0.05: Significant; p-value < 0.01: Highly significant
•: Independent t-test.

Table 3 shows the relation of the three monocytes subsets frequencies to different clinical data of MS patients. There is no statistically significant difference in the frequency of the classical and intermediate monocyte subset with any of the clinical parameters. Whereas the non-classical monocyte subset frequencies in patients with evidence of activity in MRI are significantly higher. No statistically significant difference in the frequency of the non-classical monocyte subset with the other clinical parameters was found

Table (3): Comparison of the classical, intermediate and non-classical monocytes percentages according to the clinical data of the MS patients

Parameter	(n.)	Classical monocytes		Test value	P-value	Sig.	Intermediate monocytes		Test value	P-value	Sig.	Non classical monocytes		Test value	P-value	Sig.
		Mean ± SD	Range				Mean ± SD	Range				Mean ± SD	Range			
Sex	Females (40)	61.00 ± 14.78	9.8 – 81.5	-1.299•	0.201	NS	12.15 ± 7.07	0.8 – 35.5	0.524•	0.603	NS	14.35 ± 5.71	7.6 – 38.5	1.480•	0.146	NS
	Males (4)	70.73 ± 3.99	66.7 – 76				10.25 ± 4.41	6.2 – 15				9.85 ± 6.89	0 – 15.3			
Family history	Negative (39)	61.76 ± 13.99	9.8 – 81.5	-0.254•	0.800	NS	12.07 ± 7.21	0.8 – 35.5	0.484•	0.631	NS	11.78 ± 5.75	2.4 – 30.4	1.126•	0.267	NS
	Positive (4)	63.72 ± 21.95	31.9 – 80.1				10.3 ± 3.17	8.2 – 15				8.48 ± 3.12	4.9 – 12.5			
Drug administration	Didn't start yet (9)	64.17 ± 17.12	31.9 – 81.5	0.643••	0.526	NS	10.22 ± 2.83	6.1 – 15.5	1.494	0.151	NS	10.67 ± 4.86	2.4 – 16.4	1.216•	0.234	NS
	Receiving treatment (34)	61.05 ± 9.52	9.8 – 76				13.16 ± 5.32	0.8 – 35.5				13.15 ± 5.22	3.9 – 22			
Current drug	Interferon beta (19)	59.66 ± 16.98	9.8 – 81.3	0.419••	0.742	NS	10.45 ± 8.17	0.8 – 35.5	1.152••	0.357	NS	11.21 ± 5.9	3.9 – 30.4	1.236••	0.327	NS
	Dimethylfumarate (4)	55.65 ± 12.03	45.5 – 73.1				15.68 ± 3.74	12.9 – 21.2				11.52 ± 4.54	5 – 15.4			
	Fingolimod (10)	66.44 ± 6.89	57.6 – 76				15.1 ± 7.37	6.1 – 33.2				11.07 ± 5.9	2.6 – 18.5			
	Ocrelizumab (2)	62.45 ± 2.19	60.9 – 64				11.4 ± 1.98	10 – 12.8				18.8 ± 4.53	15.6 – 22			
MRI findings (evidence of activity)	No evidence of activity (19)	66.52 ± 11.2	47.6 – 81.5	1.892••	0.073	NS	11.09 ± 6.52	2.8 – 33.2	0.808••	0.429	NS	9.09 ± 4.59	2.4 – 18.5	3.683•	0.002	HS
	Evidence of activity (3)	53.83 ± 6.04	50 – 60.8				14.2 ± 1.21	13.1 – 15.5				20.77 ± 8.42	14.8 – 30.4			

P-value > 0.05: Nonsignificant; p-value < 0.05: Significant; p-value < 0.01: Highly significant
•: Independent t-test; ••: One Way ANOVA test.

Table 4 shows no statistically significant correlation between the frequencies of the different monocyte subsets and the age, EDSS scores, duration of the disease and the number of relapses of the MS patients.

Table (4): Correlation between the frequencies of the different monocyte subsets and other clinical data of the MS patients

	Monocytes					
	Classical		Intermediate		Non classical	
	R	P-value	R	P-value	r	P-value
Age (years)	-0.043	0.782	0.108	0.487	-0.110	0.478
Neurological examination (EDSS)	-0.202	0.188	0.231	0.132	0.007	0.962
Duration of the disease (years)	0.099	0.522	0.282	0.064	-0.061	0.696
Number of activity (during last year)	-0.179	0.246	0.172	0.263	-0.011	0.942

P-value > 0.05: Nonsignificant; p-value < 0.05: Significant; p-value < 0.01: Highly significant.

Spearman correlation coefficient:

Comparison of the percentage of each monocyte subset between the relapse and remission groups among the MS patients was done and showed not statistically significant as seen in **Table 5.**

Table (5): Comparison of the monocyte subset frequencies between remission and relapse groups among the included MS patients

		Remission No. = 22	Relapse No. = 22	Test value•	P-value	Sig.
Classical monocytes	Mean±SD	63.91 ± 12.29	59.85 ± 16.26	0.934	0.356	NS
	Range	40.3 – 81.5	9.8 – 81.3			
Intermediate monocytes	Mean±SD	11.94 ± 7.59	12.02 ± 6.22	-0.039	0.969	NS
	Range	0.8 – 35.5	2 – 33.2			
Non classical monocytes	Mean±SD	13.39 ± 4.12	14.50 ± 7.30	-0.621	0.538	NS
	Range	8.8 – 24.3	0 – 38.5			

P-value > 0.05: Non significant; p-value < 0.05: Significant; p-value < 0.01: Highly significant •: Independent t-test

DISCUSSION:

Multiple sclerosis disease course is highly variable and unpredictable among individuals, especially regarding the future risk of disability progression. Despite decades of research, few reliable biomarkers have been identified for monitoring the course of MS and treatment responses. Using biological markers, it is impossible to predict which MS patients suffer a more severe disease course [7].

Characterization of the monocyte subsets in MS facilitates essential insight into disease mechanisms and potential therapeutic targets. The most recent successful therapeutic strategies involve highly specific depletion of peripheral blood cell populations such as B cells (rituximab and ocrelizumab) or prevent activated T cells from entering into the CNS (natalizumab) [8]. A similar strategy targeting monocytes or myeloid lineage cells may also have potential in MS therapy [7].

The present study showed an increase in pan monocyte percentages in RRMS patients, represented by the expansion of classical, intermediate and non-classical monocyte levels compared to healthy controls. Partially similar, ***Fischer et al. (2019)*** investigated the effects of the therapeutically relevant GC methylprednisolone on monocytes in 24 healthy individuals and 30 MS (14 RRMS, 8 SPMS, 8 PPMS) patients. They analyzed the monocyte subtypes percentages before and after administering GC methylprednisolone in the patients' group. They reported that classical $CD14^{++}CD16^{-}$ monocytes were significantly more abundant in MS patients independently of the disease activity than in healthy control subjects. At the same time, non-classical $CD14^{+}CD16^{++}$ monocytes were less frequent in MS patients. However, the percentage of intermediate CD14++ CD16+ monocytes was unaltered [9]. In addition, ***Chuluundorj et al. (2014)*** studied the level of peripheral blood monocytes in 29 healthy subjects and 20 MS patients in relapse. They stated that the relative proportions of the classical and non-classical monocyte subsets were significantly altered in MS patients compared to healthy subjects. The proportion of classical monocytes was decreased, while the proportion of non-classical monocytes showed a fivefold increase in their MS patients compared to the healthy subjects [10].

Also, ***D'Amico et al. (2022)*** reported in their prospective case–control study conducted on 52 patients recently diagnosed with RRMS that the intermediate and non-

classical monocytes displayed higher frequencies in RRMS patients when compared to healthy controls [7].

A sole increase in non-classical monocytes was revealed by ***Gjelstrup et al. (2018).*** They investigated monocytic involvement in MS and included 40 patients with incipient or activated MS and 20 healthy controls. Their study demonstrated a significant expansion of the non-classical monocyte population in patients with MS compared to healthy controls. A proportionate reduction in the classical monocyte population accompanied the increase in non-classical monocytes [5]. In contrast, ***Waschbisch et al. (2016)*** examined the frequency and phenotype of monocyte subpopulations in peripheral blood and CSF of 40 RRMS patients and 40 healthy controls. They provided evidence for reducing the intermediate and non-classical monocyte percentages in the peripheral blood of RRMS subjects compared to healthy controls. The decrease in the circulating non-classical monocyte population may be secondary to poor recruitment from the bone marrow, an imbalanced monocyte differentiation process, or compartmentalization of these cells to the CNS [11].

The apparent discrepancy between studies is likely due to the composition of the different patient cohorts with other disease activities and the difference in treatment plans and administration. In addition, it is currently widely assumed that blood monocyte subsets represent stages in a developmental sequence, with non-classical monocytes being considered the more mature monocytes [12].

In the current study, there were no significant differences in monocyte subsets regarding clinical disease activity, similar to ***Fischer et al. (2019),*** who did not observe any differences concerning the abundance of monocyte subsets regarding the disease activity[9]. In contrast, ***Haschka et al. (2020)*** studied the expansion of neutrophils and classical and non-classical monocytes in 70 MS patients and 15 healthy controls. They found an increase in classical monocytes in RRMS patients in remission compared to those in activity with increased non-classical monocytes [13]. Also, they reported that alterations of non-classical monocyte levels were associated with the plethora of MS [13].

As regards MRI findings of activity, the present study found that RRMS patients with evidence of activity in MRI had a significant increase in the non-classical monocyte percentages than patients with no evidence of activity, unlike ***Gjelstrup et al. (2018),*** who found that the monocytes subtypes were not correlated with the MRI findings [5].

The present study used EDSS and the number of attacks during the last year to assess patients' disabilities and disease severity. In our RRMS patients, the monocyte subtypes did not correlate with the degree of disability by EDSS nor the number of relapses during the last year. This finding goes along with ***Gjelstrup et al. (2018), D'Amico et al. (2022)*** and ***Haschka et al. (2020),*** who concluded that the monocyte subsets had no correlation with the degree of disability detected [5,7,13].

Our study found no correlation between DMT administration and monocyte subsets. Similarly, ***Haschka et al. (2020)*** found no effect of DMT administration on the monocyte subset distribution pattern [13]. Also, ***Fischer et al. (2019)*** found that monocyte subsets remained unaltered by glucocorticoid treatment concerning short- and long-term effects [9].

However, ***Savinetti et al. (2021)*** stated that increased percentages of intermediate and non-classical monocytes were found in IFN-β–treated RRMS patients exceeding the levels of these subpopulations in both

untreated RRMS patients and healthy controls[14].

In conclusion, our study found that the three monocyte subsets (Classical, Inter-mediate & non-classical) also increased significantly in MS patients in relapse and remission. These results denote the vital role of monocytes in disease pathology, and they might be related to disease activity, especially the non-classical subset. This makes monocytes a promising therapeutic target and a possible diagnostic tool.

Conflict of Interest:

There was no conflict of interest.

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الانواع الفرعية للخلايا وحيدات النواه فى مرضى التصلب المتعدد النوع الانتكاسي المتكرر في مصر

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الخلفية: على الرغم من أن العديد من أنواع الخلايا المناعية متورطة في تقدم مرض التصلب المتعدد ، يُعتقد أن الخلايا وحيدة النواه النشطة هي واحدة من أولى الخلايا التي تصل إلى الدماغ وتبدأ الالتهاب. ومع ذلك ، لا يُعرف الكثير عن كيفية مشاركة مجموعات الخلايا أحادية النواه (كلاسيكية ومتوسطة وغير كلاسيكية) في مرض التصلب المتعدد.

الهدف من العمل: تهدف الدراسة الحالية إلى التحقق من وجود مجموعات فرعية مختلفة من الخلايا أحادية النواه في مرضى التصلب المتعدد النوع الانتكاسي المتكرر المصريين وعلاقتها بنشاط المرض.

المرضى والطرق: تضمنت هذه الدراسة 44 مريضًا, 22 مريض في حالة انتكاس ، و 22 مريضً في حالة السكون ، تم تشخيصهم وفقًا لمعايير MacDonalds لعام 2017 ، و 44 من الاصحاء المتطابقين مع العمر والجنس. تم أخذ التاريخ الشخصي والطبي الكامل من المرضى وتم عمل مقياس حالة الإعاقة الموسع (EDSS) لتقييم إعاقة المرضى. تم توصيف المجموعات الفرعية من الخلايا وحيدات النواه عن طريق قياس التدفق الخلوي لجميع المشاركين.

النتائج: أظهرت النسبة المئوية لمجموعات الخلايا وحيدات النواه الكلاسيكية والمتوسطة وغير الكلاسيكية زيادة ذات دلالة إحصائية في مرضى التصلب المتعدد مقارنة بالاصحاء ذات القيم (0.029، 0.049، 0.043) على التوالي. لا يوجد فرق معتد به إحصائيًا في تواتر مجموعات الخلايا وحيدات النواه الكلاسيكية والمتوسطة مع أي من المعلمات السريرية. ومع ذلك ، فإن المرضى الذين لديهم دليل على نشاط في التصوير بالرنين المغناطيسي لديهم تواتر مرتفع بشكل ملحوظ من الخلايا وحيدات النواه غير الكلاسيكية بقيمة (0.002) . لا يوجد فرق معتد به إحصائيًا في تواتر المجموعة الفرعية الغير كلاسيكية مع المعلمات السريرية الأخرى.

الخلاصة: في حالة الانتكاس والسكون من مرض التصلب المتعدد ، تزداد المجموعات الفرعية للخلايا وحيدات النواه الثلاث (الكلاسيكية والمتوسطة وغير الكلاسيكية) زيادة كبيرة. تشير هذه الزيادة إلى الدور الحيوي للخلايا ا وحيدات النواه في المرض ، حيث قد تكون مرتبطة بنشاط المرض ، خاصة النوع الغير كلاسيكي. هذا الاكتشاف يجعل الخلايا وحيدات النواه هدفًا علاجيًا واعدًا وأداة تشخيصية محتملة لمرض التصلب المتعدد.