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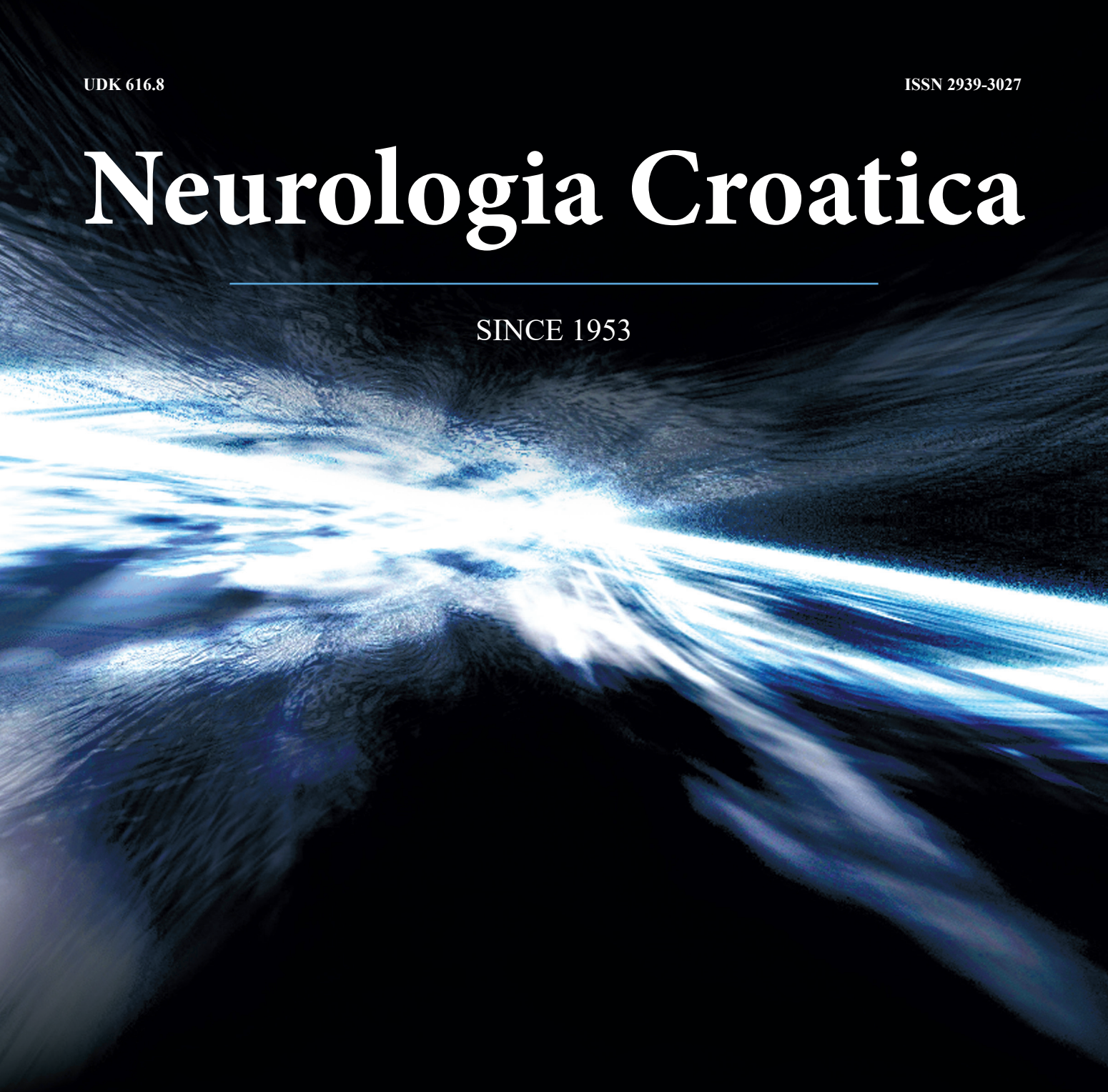

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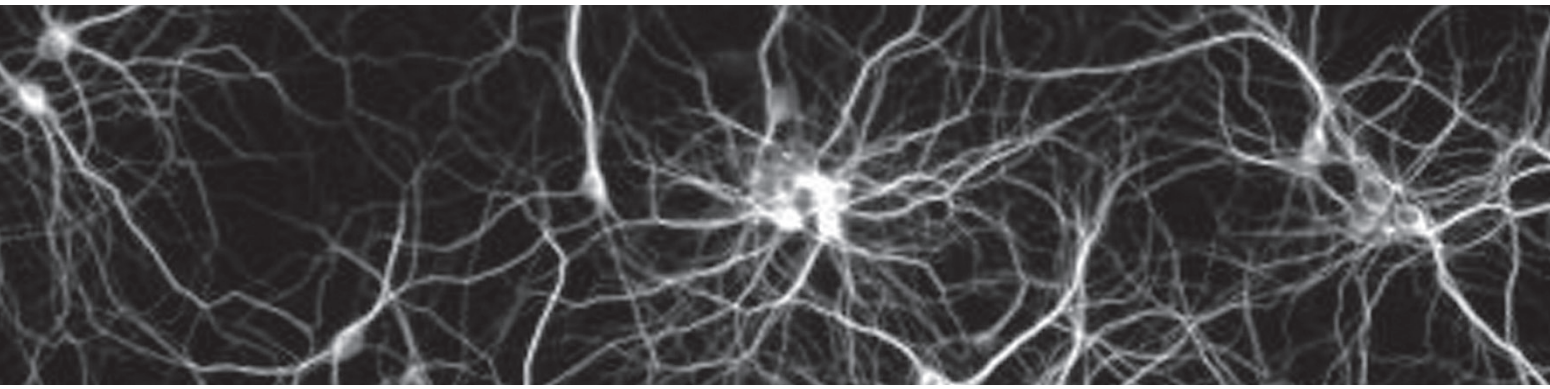


Editorial

The June 2025 issue of *Neurologia Croatica* offers a compelling cross-section of contemporary neurology, spanning the precision of endovascular intervention, the evolving safety profile of disease-modifying therapies in multiple sclerosis (MS), and the deeply human realities of living with a chronic neurological condition. Each of the three manuscripts featured in this issue contributes uniquely to both the scientific and clinical discourse, illustrating the multidisciplinary demands and ethical considerations that increasingly define our field.

We open with the article by Franić *et al.*, *"Efficacy and Safety of Carotid Stenting – A Single Center Experience"*, which addresses an enduring debate in vascular neurology: the role of carotid artery stenting (CAS) versus carotid endarterectomy (CEA) in stroke prevention. In this retrospective study of 109 patients treated between 2018 and 2020, the authors provide robust institutional data showing low rates of both early and late complications following CAS. The analysis reveals that hemodynamically significant stenosis was the only factor significantly associated with early procedural outcomes, and no single variable significantly influenced long-term success.

What stands out in this report is not only the encouraging safety and efficacy profile of CAS but also the reflection of a larger trend in stroke prevention: individualized, risk-adapted therapy in high-volume centers. As stenting technologies advance and neurointerventional teams gain experience, it is becoming increasingly clear that CAS, when performed in optimal settings, can rival the gold-standard outcomes of CEA—especially for patients who are poor surgical candidates. This study affirms the importance of center experience and rigorous patient selection, underscoring that innovation in procedural neurology must always be paired with careful clinical judgment.

The second article, *"The Quality of Life in People with Multiple Sclerosis in Varaždin County"* by Sokol *et al.*, offers a powerful sociomedical lens into the lived experience of MS in a specific Croatian region. This cross-sectional study of 46 MS patients illuminates the complex interplay between education, emotional well-being, family dynamics, and social integration. The findings point to a concerning persistence of stigmatization, with patients frequently retreating into the private sphere for support. Notably, the study found that individuals with higher levels of education reported better mental hygiene and fewer emotional challenges—suggesting that educational attainment may offer protective effects against the psychological burden of MS.

This work resonates far beyond its regional focus. It reminds us that neurological disease management cannot be confined to pharmacology or imaging. For patients with chronic diseases like MS, quality of life is shaped as much by social and emotional scaffolding as by biological interventions. Depression, anxiety, impaired work capacity, and disrupted family planning are not peripheral issues—they are central to patient outcomes and should inform how we deliver care.

Moreover, this study has clear implications for health policy and public health planning. It highlights the need for targeted community interventions to combat stigma, enhance social support networks, and improve access to psychosocial services. The link between education and emotional resilience identified in this study also suggests a role for patient education initiatives in therapeutic planning. In light of these findings, neurologists are urged to engage more actively with multidisciplinary teams, including psychologists, social workers, and occupational therapists, to address the full spectrum of needs in people with MS.

The final article, a case report by Piskač *et al.*, brings us into the realm of neuroimmunology with a critical reminder of the double-edged nature of immunosuppressive therapies. Titled *"Association of Alemtuzumab Treatment with Lymphoma Development in a Patient with Relapsing-Remitting Multiple Sclerosis"*, this report describes a patient who developed diffuse large B-cell lymphoma (DLBCL) several years after participating in a clinical trial for alemtuzumab. While alemtuzumab has demonstrated transformative efficacy in treating relapsing-remitting multiple sclerosis (RRMS), it also poses significant risks—including secondary autoimmunity and, as increasingly discussed in the literature, potential malignancy.

Although a direct causal relationship between alemtuzumab and lymphoma remains speculative, this case adds weight to growing concerns in post-marketing surveillance. It also raises essential ethical and clinical questions: How should we counsel patients about rare but serious long-term risks? What are the limits of informed consent when long-term data are incomplete? And how can we balance disease modification with patient safety in an already vulnerable population?

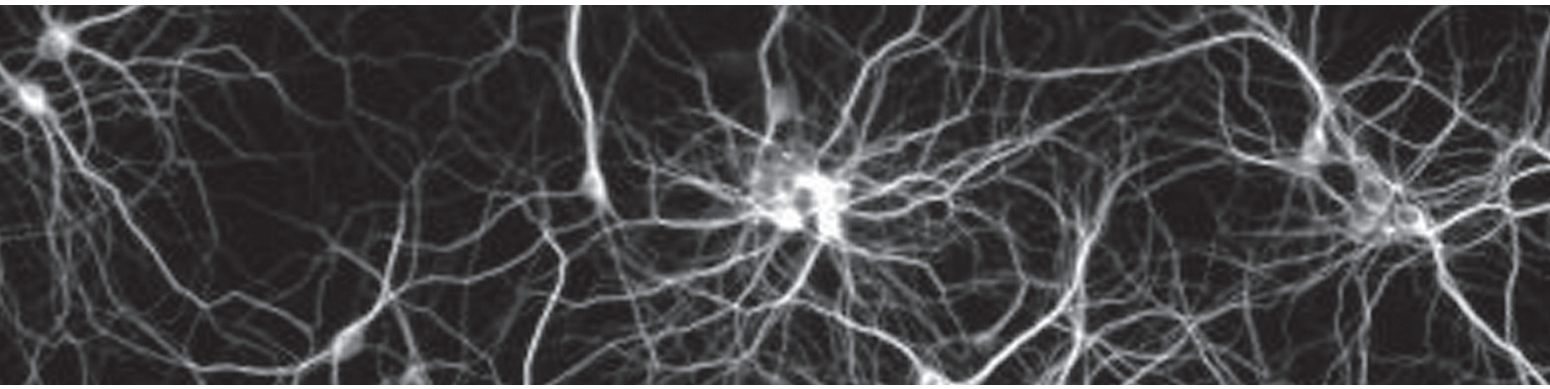
This report also serves as a valuable cautionary tale in an era of rapidly expanding therapeutic options for MS. As our arsenal of disease-modifying therapies grows, so too must our frameworks for long-term monitoring, patient selection, and shared decision-making. Rare adverse events—though statistically minimal—carry enormous personal and clinical weight. By documenting such events with scientific rigor, case reports like this one contribute to pharmacovigilance and improve collective understanding of the long-term impact of biologic therapies.

Taken together, the three manuscripts featured in this issue underscore a central theme: modern neurology is inherently interdisciplinary, spanning high-technology interventions, immune-modulating therapies, and socio-emotional dimensions of chronic illness. They also reflect the evolving responsibilities of the neurologist—not merely as a diagnostician or proceduralist, but as a steward of long-term patient well-being in all its complexity.

Looking ahead, several opportunities emerge. In vascular neurology, the development of real-time risk stratification tools for CAS could further personalize therapy and improve outcomes. In MS care, large-scale registries could better capture long-term safety data for high-efficacy therapies like alemtuzumab, helping clinicians make more informed decisions. And finally, we must redouble our efforts in addressing the non-biological determinants of health—stigma, education, and access to care—especially in resource-limited settings.

In conclusion, this issue of *Neurologia Croatica* reminds us that excellence in neurology requires integration of science and compassion, innovation and vigilance, and the cellular with the societal. We thank our contributors for their thoughtful, data-driven work, and we hope these articles inspire reflection, inquiry, and progress in your own clinical and academic endeavors.

Mario Habek
Editor-in-Chief



Efficacy and safety of carotid stenting: a single center experience

Ivana Karla Franić[1], Magdalena Krbot Skorić[1,2], David Ozretić[2,3], Ivan Jovanović[3], Danilo Gardijan[3], Josip Ljevak[1], Ivan Perić[1], Katarina Starčević[1], Antonela Bazina Martinović[1,2], Zdravka Poljaković-Skurić[1,2]

ABSTRACT – *Background and purpose:* Treatment of symptomatic or high-grade internal carotid artery (ICA) stenosis is an important method in stroke prevention. In recent years the focus has been shifting to carotid artery stenting (CAS) as an equally effective and safe method as carotid endarterectomy (CEA) for internal carotid artery (ICA) stenosis treatment, especially in high-volume centers. *Methods:* We did a retrospective single-center study and included a total of 109 patients who had symptomatic and/or hemodynamically significant ICA stenosis and were treated at our center from 2018-2020. Stenosis was exclusively caused by atherosclerosis. Stenosis severity was measured angiographically and with carotid duplex ultrasound and calculated by NASCET criteria. We analyzed the demographical, clinical, neurosonological and angiographical characteristics of our patient cohort. *Results:* The primary endpoint was to determine rates of early and late complications after CAS. Complications were defined as clinical (recurrent TIA/stroke) and neurosonological (stent restenosis verified by ultrasound). We had low rates of both early and late complications, especially in terms of clinical complications. The secondary endpoint was to determine risk factors associated with complications after CAS. Statistical analysis showed that, out of all included parameters, only hemodynamically significant stenosis had a statistically significant impact on early CAS outcomes. *Conclusions:* Our complication rates were low, and no statistically significant impact on long-term CAS outcomes for any of the included risk factors was found. Our results were similar to current literature data on both CAS and CEA efficiency. CAS is an efficient and safe treatment option for ICA stenosis in carefully selected patients.

Keywords: carotid artery stenting, ischemic stroke, neuroradiology, carotid stenosis, neurointervention, atherosclerosis

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INTRODUCTION

Treatment of symptomatic or high-grade carotid artery stenosis is considered an important method in stroke prevention, as carotid disease is a cause of at least 20% of strokes. Carotid endarterectomy (CEA) is still the first-line treatment option for carotid artery stenosis, being a safe and well-explored method of treatment. Carotid artery stenting (CAS) on the other hand, was reserved for patients with comorbidities that could not warrant surgical treatment, patients with unfavorable neck anatomy, patients with contralateral carotid occlusion and as a second option in case of restenosis after CEA. In recent years, the focus has been increasingly shifting to CAS, an equally effective and safe method of treatment, especially in high-volume centers. This is mainly because of the shorter convalescence time and generally more sparing effect of the method. (1,2) Despite numerous randomized clinical trials being conducted, a distinctly superior method has not yet been determined. (1,2)

In our retrospective study, we present a single-center experience of carotid artery stenting with a follow-up for at least one year.

MATERIAL AND METHODS

STUDY DESIGN AND PATIENT SELECTION

We conducted a retrospective single-center study in patients with symptomatic and/or hemodynamically significant carotid artery stenosis who were treated with CAS in the Neurological Intensive Care Unit (NICU) of University Hospital Center (UHC) Zagreb for two years (January 2018 – January 2020). The ethics committee of UHC Zagreb approved the study in November 2020. In our study, we analyzed the preoperative demographic, clinical, neurosonological, and angiographical characteristics of our patients. The inclusion criteria for patient selection was carotid artery stenosis caused by atherosclerosis, as all other causes were excluded. Stenosis severity was measured both angiographically and with carotid duplex ultrasound and calculated by NASCET criteria for internal carotid artery (ICA) stenosis. CAS was performed in patients with symptomatic ICA stenosis, and asymptomatic patients with hemodynamically significant stenosis. Inclusion criteria for symptomatic patients was a history of ischemic stroke (IS) or transitory ischemic attack (TIA) caused by carotid artery atherosclerosis, after exclusion of other causes of stroke or TIA. In those patients, CAS was performed if carotid artery stenosis was 50-99% by NASCET criteria. For asymptomatic patients, the inclusion criteria for performing CAS was hemodynamically significant stenosis, e.g., 70-99% stenosis according to NASCET criteria.

Our patients were given single antiplatelet therapy (in most cases clopidogrel) at least 5 days before the procedure and dual antiplatelet therapy (DAPT) immediately after the procedure. DAPT (aspirin and clopidogrel) was given during the first three months post-procedurally and after that period only aspirin as a long-term antiplatelet therapy. If the patient was a non-responder to the standard first-line antiplatelet therapy, ticagrelor was introduced as a second-line antiplatelet therapy of choice instead of clopidogrel. As non-responders, we defined patients who did not have adequate platelet inhibition measured by aggregometry on the VerifyNow device and expressed in platelet reactivity units (PRU) higher than 208.

OUTCOMES AND ENDPOINTS

The primary outcomes in our study were early and late complications of CAS. Early (periprocedural) complications were defined as clinical, sonological or angiographical worsening in the first 24 hours post procedurally. Late (postprocedural) complications we defined as progression of stenosis on ultrasound in comparison to the initial sonological finding, or as repeated IS/TIA of the same etiology during our follow-up period.

The follow-up period was up to 54 months postoperatively. For all patients enrolled in the study, the follow-up included control carotid ultrasound and neurological examination. These control visits were scheduled after 3, 6, and 12 months postoperatively during the first year of the follow-up period. After the first year, control visits were approximately every 6 or 12 months. Our results were expressed descriptively and with a Modified Ranking Scale (mRS).

Our secondary aim was to define risk factors for long-term complications, and the effect of predicted risk factors on the clinical outcome or stent restenosis after CAS during the long-term follow-up. We assessed preexisting main risk factors for atherosclerosis – hypertension, hyperlipidemia and diabetes mellitus and categorized our patients according to whether they had only one, a combination of two or all three risk factors. The presence

of symptomatic stenosis and/or hemodynamically significant stenosis and the state of contralateral ICA were also included in the analysis, as well as atrial fibrillation (AF) and previous IS and/or TIA. Finally, we analyzed the outcomes based on the choice of long-term dual antiplatelet therapy (DAPT).

STATISTICAL METHODS

Statistical analysis was performed using SPSS 25 software (IBM, USA). The Kolmogorov-Smirnov test was performed to assess the distribution of the data. Qualitative variables were described in the form of absolute number and percentage, while quantitative variables were described in the form of mean ± standard deviation or median (range), according to the distribution. Logistic regression analysis was performed to determine which variables are statistically significant predictors for specific outcomes. P values of less than 0.05 were considered significant.

RESULTS

GENERAL DATA AND PARAMETERS

According to the selection criteria, we included a total of 109 patients in this study, 89 men (81,7%) and 20 women (18,3%). The average age of our cohort was 68,32 ± 8,531 years. Risk factors for atherosclerotic disease and/or IS included in the analysis, and their occurrence in the cohort are shown in Table 1.

Stenosis severity was measured both with carotid Doppler ultrasound and CT angiography. We had no patients with Grade 1 stenosis (<50% stenosis by NASCET), Grade 2 stenosis (50-70%) was detected in 20 patients (18,3%), Grade 3 stenosis (71-90%) was present in 46 patients (42,2%) and 39 patients (35,8%) had Grade 4 stenosis (>90%). In 4 cases (3,7%), no data on stenosis grade was available.

Further details on all main demographic data and clinical characteristics of our patients are shown in Table 1.

Table 1. *Demographic and clinical data*

Included parameters	Number of patients (n)	Percentages (%)
Male sex	89	81,7%
Arterial hypertension	102	93,6%
Hyperlipidemia	57	52,3%
Diabetes mellitus	37	33,9%
Previous TIA	15	13,8%
Previous ischemic stroke	72	66,1%
Atrial fibrillation	9	8,3%
Symptomatic stenosis	64	58,7%
Asymptomatic, but high-grade stenosis	45	41,3%
Hemodynamically significant stenosis*	100	91,7%
Not hemodynamically significant, but symptomatic*	5	4,6%
Contralateral ICA (stenosis/occlusion)[a]	44	40,4%
Transition from clopidogrel to ticagrelor[b]	15	13,8%

Table 1 shows all main demographic data and clinical characteristics of our cohort that were included in the statistics. For each parameter, the number and the percentage of affected patients were shown.

a) In 59 patients (54,1%) contralateral ICA had regular flow through the vessel, 21 patients (19,3%) had some grade of stenosis in contralateral ICA and 23 patients (21,1%) had contralateral ICA occlusion. In 6 cases (5,5%) contralateral ICA had already been previously treated with CAS/CEA. b) Considering postprocedural therapy, 92 patients (84,4%) received standard first-line DAPT (ASA + clopidogrel), 15 patients (13,8%) needed to be transferred to second-line treatment (ASA + ticagrelor), and for 2 people (1,8%) the data on received medical treatment after CAS was not available.

* In 4 cases (3,7%) no data on stenosis hemodynamic was available.

EARLY COMPLICATIONS

Early (periprocedural) complications were defined as clinical, sonological or angiographical worsening in the first 24 hours after CAS. We had 4 (3.6%) patients with periprocedural complications – types and quantity of complications are shown in Table 2. No clinical neurological complications (TIA or IS) were observed. In another 4 cases (3,6%) angiographically verified significant residual stenosis persisted despite successful procedure, i.e., successful stent placement.

Functional outcome was analysed using mRS. The initial mRS score was evaluated at the time of the patients' discharge from the hospital. (Chart 1). One patient was immediately transferred to another hospital after the procedure, so we did not have any data on the mRS score at the time of discharge.

LATE COMPLICATIONS

Late complications were defined as clinical complications (TIA/IS of the same etiology) and sonological complications (stenosis progression in the placed stent verified on carotid Doppler ultrasound) during the follow-up period.

Follow-up visits were scheduled 3, 6 and 12 months after CAS during the first year, but our follow-up extended beyond the first year as well. The first follow-up visit after the first postprocedural year was on average 24 months after the procedure, i.e., one year after previous control visit.

After that, control visits were on average 31-, 41- and 45 months post-procedurally. On those visits, we had 27-, 16-, 3- and 2 patients respectively.

Table 2. *Descriptive analysis of periprocedural (early) complications*

Periprocedural complications	Number of patients (n)	Percentages (%)
ICA dissection	1	0,9%
Thrombus formation	1	0,9%
Complication of puncture site	2	1,8%

Table 2 shows absolute number and the percentage of patients for each type of periprocedural (or early) complications in our cohort in the first 24 hours after stenting. We encountered with one ICA dissection, one thrombotic complication and two puncture site complications.

Chart 1. *mRS scores at discharge and at every visit during the follow up*

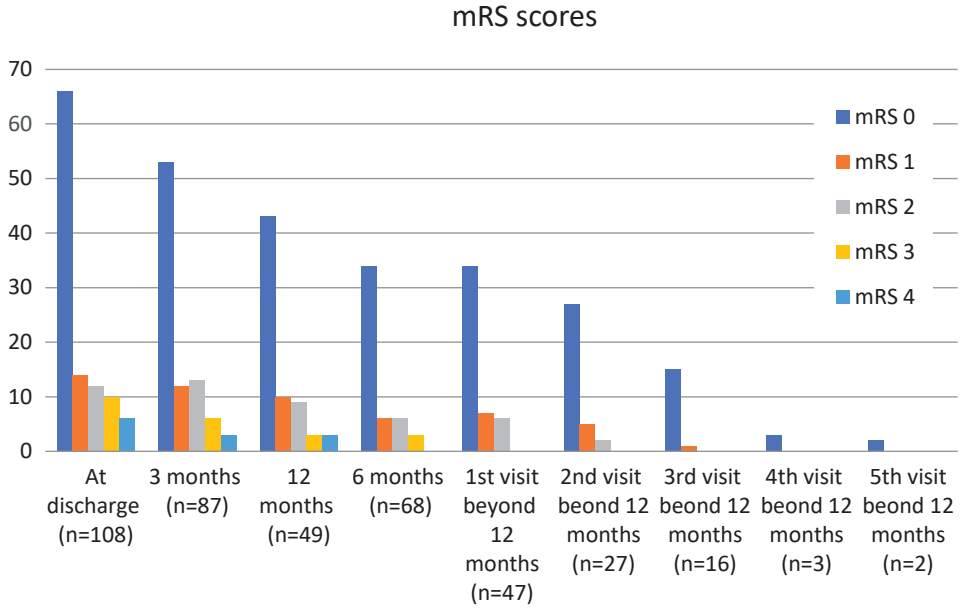

Chart 1 shows mRS scores at every follow-up visit. In the chart mRS scores are shown quantitatively. We also did an analysis of mRS scores and expressed the results as median value of distribution for every visit. At discharge and at every follow-up visit median mRS was 0,00.

The data on the rates of observed clinical and sonological complications, as well as the absolute number and the percentage of patients on each follow-up visit is shown and described in Table 3.

LOGISTIC REGRESSION ANALYSIS

A secondary aim of our study was to determine whether any of the predicted risk factors or parameters included in the analysis had any impact on early and long-term CAS outcomes. The results of the statistical analysis are shown in Table 4.

Out of all analyzed parameters, only hemodynamically significant stenosis had a statistically significant impact on the periprocedural outcomes of CAS.

DISCUSSION

The stenosis of ICA occurs in 4–7% of middle-aged and older adults. ICA stenosis represents a major component of the estimated circa 20% of strokes directly attributable to cerebrovascular disease (2). The main risk factors associated with this condition include arterial hypertension, diabetes mellitus, hyperlipidemia, and chronic coronary vessel disease, with a clear male predominance (3).

We reported logistic regression analysis for outcomes of early (periprocedural) complications and late sonological complications after 3 and 6 months after CAS because, for all other observed outcomes on all other control visits, there were too few complications or too few patients left in the follow up to do a proper statistical analysis. No statistically significant impact on long-term CAS outcomes for included risk factors was found (except for hemodynamically significant stenosis on periprocedural outcomes) since the number of complication events through the follow-up was too low to account for statistically significant results.

The incidence of CAS complications is most often compared to outcomes after CEA, as CEA is a well-established method, known for safety. We compared our results on CAS with current data from the literature for CAS and for CEA as well, in terms of early complications, late complications and rates of restenosis.

EARLY COMPLICATIONS

In current literature, most often analyzed and reported early complications after either CAS or CEA are periprocedural stroke, myocardial infarction (MI) or death outcome. In our cohort, we had

Table 3. *Descriptive analysis of late (postprocedural) complications*

	Number of patients	Late clinical complications	Late sonological complications
3 months after CAS	87 (79,8%)	2 (2,3%) [a]	6 (6,9%) [b]
6 months after CAS	68 (62,4%)	0 (0.0%)	8 (11,8%) [c]
12 months after CAS	49 (45,0%)	0 (0.0%)	4 (8,2%) [d]
First visit after 12 months	47 (43,1%)	1 (2,1%) [e]	3 (6,4%) [f]
All other visits up to the end of follow-up	≤ 27 (≤ 24,8%)	0 (0.0%)	0 (0.0%)

Table 3 shows absolute numbers and percentages of late, or postprocedural complications after CAS in the long-term follow-up, as well as the number of patients on each follow-up visit.

a) Both patients had clinical complications in the form of TIA.

b) Out of 6 patients who have had a certain degree of stenosis progression in the placed stent, there were 4 cases (4,6%) of moderate stenosis (50-70%) and in 2 patients (2,3%) there was significant stenosis present and balloon dilatation of the stent was needed. All 6 patients were asymptomatic.

c) Out of 8 patients with sonological complications, there were 5 cases (7,4%) of moderate stenosis and 2 (2,9%) patients with significant stenosis who later underwent stent dilatation. All patients were asymptomatic.

d) Out of 4 patients who had sonological complications, there was 1 mild stenosis (30-40%), 1 moderate stenosis and 1 severe stenosis (75%). In 1 case there was progression of previously significant restenosis of the stent. All the patients were asymptomatic.

e) The only patient who had clinical complication on this follow-up visit had a repeated IS. Nevertheless, the neurological deficit completely subsided, and he has been discharged without any focal neurological deficit.

f) Out of 3 patients that had sonological complications on ultrasound, 2 were moderate stenoses and 1 verified in-stent thrombosis which developed between two visits. This patient was asymptomatic despite in-stent thrombosis. Of the other two, one was the patient with repeated IS.

Table 4. *Logistic regression analysis*

	Univariable logistic regression		
	Exp(B)	95% C.I. for EXP(B)	p value
Outcomes after CAS (periprocedural complications)			
Sex	0.000	0.000	0.998
Age	0.953	0.876-1.038	0.273
Hyperlipidemia	2.941	0.566-15.271	0.199
Diabetes Mellitus	0.629	0.120-3,279	0.582
Previous TIA	0.000	0.000	0.999
Previous ischemic stroke	1.591	0.305-8.300	0.582
Atrial fibrillation	4.476	0.759-26.411	0.098
Symptomatic stenosis	1.186	0.269-5.238	0.821
Hemodynamically significant stenosis	0.096	0.013-0.687	0.020
Transition from clopidogrel to ticagrelor	2.205	0.402-12.110	0.363
Neurosonological complications 3 months after CAS (progression of stenosis verified on carotid color Doppler ultrasound)			
Sex	0.813	0.089-7.448	0.854
Age	0.946	0.851-1.052	0.307
Hyperlipidemia	0.380	0.066-2.197	0.280
Diabetes Mellitus	0.359	0.040-3.219	0.360
Previous TIA	1.600	0.168-15.273	0.683
Previous ischemic stroke	193856981,040936	0.000	0.998
Atrial fibrillation	0.000	0.000	0.999
Symptomatic stenosis	4.205	0.470-37.610	0.199
Hemodynamically significant stenosis	129237994,288251	0.000	0.999
Transition from clopidogrel to ticagrelor	3.889	0.621-24.335	0.147
Neurosonological complications 6 months after CAS (progression of stenosis verified on carotid color Doppler ultrasound)			
Sex	2.400	0.502-11.477	0.273
Age	0.935	0.848-1.032	0.181
Hyperlipidemia	0.765	0.175-3.349	0.722
Diabetes Mellitus	1.114	0.242-5.128	0.889
Previous TIA	0.929	0.100-8.580	0.948
Previous ischemic stroke	0.500	0.113-2.210	0.361
Atrial fibrillation	0.000	0.000	0.999
Symptomatic stenosis	0.579	0.132-2.548	0.470
Hemodynamically significant stenosis	230782043,728727	0.000	0.999
Transition from clopidogrel to ticagrelor	1.815	0.315-10.455	0.505

Table 4 shows the results of the logistic regression analysis of our data. Statistical analysis showed that out of all included parameters, only hemodynamically significant stenosis turned out to have a statistically relevant impact on the periprocedural outcome of CAS (OR 0.096, 95% C.I. 0.013-0.687, p=0.020), as it was shown that patients with hemodynamically significant stenosis had a higher chance for successful CAS procedure and lower early complications rates. Hemodynamically significant stenosis did not have this correlation with CAS outcomes on long-term follow-up visits, as those results were not statistically significant. For all the other included parameters (risk factors), the statistical analysis did not show any statistically significant cause-effect relationship on either periprocedural or long-term outcomes of CAS.

4 cases of periprocedural complications (3,6%), all in the form of access site complications.

One CAS-only single-center study reported 6,7% rate of access site complications, which is significantly higher than our 1,8% puncture site complications. During the in-hospital stay, they reported 2,0% of non-disabling strokes, 0,9% of disabling strokes and 0,9% of TIA observed (3), while none of our patients developed TIA or IS (major or minor) during the hospitalization up to the time of discharge.

In the CAVATAS study, CREST and ICSS trial, CAS was associated with lower risks of cranial nerve palsy, periprocedural neurological injury (stroke plus cranial nerve injury) and access site hematoma than CEA in the periprocedural period (5,6,7,8,9,10,11,12).

Studies report that the aggregated efficacy/safety outcome (composite outcome of periprocedural death, stroke, MI, or non-periprocedural ipsilateral stroke) was not significantly different between CAS and CEA (11,15). Moreover, there were no significant risk factors or effect modifiers found for the periprocedural death or stroke for symptomatic carotid stenosis undergoing CAS or CEA (11,17), not even stenosis greater than 90% (17). In our study, we also did not find that significant stenosis or other risk factors had any statistically significant impact on CAS outcomes in terms of stroke.

One study reports that associated periprocedural stroke was significantly higher with CAS than CEA, which was mainly attributable to non-disabling or minor strokes (11), the finding which was confirmed by EVA-3S, CREST and ICSS trials (6,10,12,13,14,18). Higher rates of periprocedural stroke after CAS could be due to dislodging the emboli during the procedure (4). However, recent advances in the use of emboli protection devices, dual antiplatelet therapy, and mesh-covered stents may decrease the risk of strokes following CAS in the future (11,18).

Regarding major events, the EVA-3S study found that the 30-day incidence of disabling stroke or death was significantly lower after CEA (8), while other studies show that the risk of associated periprocedural major stroke or mortality rate was not different between groups (11). Also, CAS was associated with a decreased risk of periprocedural MI in several studies (7,11,12,13).

LATE COMPLICATIONS

Late complications in studies in the literature are the development of recurrent ipsilateral IS (both major and minor stroke) or death during the follow-up period.

The rates of late complications in our study were low, with a total of 3 (2,75%) of patients with post-procedural clinical complications in the entire follow-up period.

One CAS-only single-center study reports 8 strokes and 3 TIAs (3.2%) during the long-term follow-up. This is a slightly higher rate, but nevertheless similar to 2,1% of late clinical complications such as stroke reported in our study in the long-term follow-up (in the second year after CAS). They did not manage to identify any predictive risk factors for long-term ipsilateral neurological complications (4), and neither did we.

Findings given by the SPACE and CREST trial and Lexington study report that once the perioperative period had passed, there was no difference in rates of late ipsilateral IS suggesting that both methods are equally effective in preventing recurrent stroke in the long-term follow-up (9,10,11,12,13,14,16,18,19,20).

Moreover, the ICSS, EVA-3S and SPACE trial and CaRESS study showed no significant differences in cumulative long-term rates of fatal or disabling stroke between CAS and CEA for symptomatic patients (5,12) and in the associated risk of long-term mortality between the two methods (6,11,18).

In terms of DAPT influence on long-term CAS outcomes, a PRECISE-MRI is a recently conducted trial that wanted to show that ticagrelor in addition to aspirin was superior to clopidogrel and aspirin combination in preventing recurrent stroke in patients undergoing CAS. In the initial results of this trial, ticagrelor has been shown to reduce the number of ischemic lesions and total ischemic lesion volume. Despite the overall fewer strokes that occurred in the ticagrelor group, the difference was not significant. However, in this study patients were randomly allocated to the ticagrelor or clopidogrel group, without any regard for their responder status. In our study, we found that the type of DAPT had no statistically significant impact on CAS outcomes. This difference in produced results could arise from the fact that our patients were being transferred to ticagrelor only if proved non-responders to clopidogrel.

THE RATES OF RESTENOSIS

In our study, rates of restenosis of the stented carotid were low, considering most of them were mild to moderate stenoses and did not progress to the stage of significant restenosis of the treated artery.

In one similar CAS-only single-center study, 8,7% developed in-stent restenosis during a follow-up of 8 months, which is significantly higher than our 2,9% during 6-month follow-up (3). In another CAS-only single-center study, stent restenosis was assessed in 4,4% of the patients in the long-term follow-up, which is similar to 6,4% on the 2-year follow-up visit in our study (4). In addition, the authors found no risk factors that were related to the occurrence of stent restenosis (4), and neither did we in our study. Nevertheless, results such as these are difficult to interpret given the small number of recurrent events and restenosis.

CAVATAS study showed similar periprocedural restenosis rates between CAS and CEA but a higher risk of severe carotid restenosis or occlusion after CAS during the long-term follow-up, which was also reported in the SPACE trial (12). However, the EVA-3S trial, ICSS study and CREST trial did not find evidence of differences in the long-term rates of severe restenosis or occlusion after CAS as compared to CEA (5,12).

The CREST and ICSS studies concluded that >70% restenosis after CAS did not increase late ipsilateral stroke risk, unlike after CEA. (9,16) The SPACE and EVA-3S trials reported no differences in ipsilateral stroke in people with restenosis compared with people without restenosis in either treatment group (9).

LIMITATIONS OF THE STUDY

There are several limitations to this study. First of all, it is a retrospective study, so it might be biased accordingly. Furthermore, in spite of the fact that our study had an almost 5-year follow-up, but for very few patients, since most patients stopped coming to the follow-up visits after some time (mostly two years after the procedure). With our hospital being the main center for endovascular treatment of carotid stenosis in Croatia, patients from all over Croatia are sent to our hospital for CAS. Most of those patients choose to do these further regular check-ups in their regional hospitals, which is one of the reasons why the number of patients is decreasing with every follow-up visit. Conclusively, in future studies, a larger number of patients should be followed for a longer period of time.

Also, this study has a limitation of a single-center study. A larger patient cohort can be accomplished by doing a multi-center studies or pooling results for the CAS registry. Forming such registries should be an advisable priority in the future.

We observed a significant gap in follow-up visit attendance during the peak of the Covid pandemic in 2020 since our inclusion time period for CAS procedures was from 2018-2020. For possible better results, the time period taken for analysis should maybe have been prolonged and CAS cases done after January 2020 also be included in the study.

In our study, we did not manage to produce a statistical analysis for all observed outcomes. However, we attributed this to the low complication rates in our study. Low rates of both clinical and sonological complications may relate to the fact that in our center CAS is performed rather routinely, giving our personnel significant expertise, which consequently makes CAS a safe and well-established treatment method in our center.

Finally, our study doesn't have a control group. In other larger, predominantly multicenter studies, CAS outcomes are mostly compared to CEA outcomes, and patients undergoing CEA were used as a control group, as it is a well-established method with known low complication rates. Ideally, as it was shown in some studies, the best medical treatment could be included as a third arm, especially in patients with asymptomatic carotid artery disease. Also, the authors are aware that for future research it would be beneficial to plan analyses of the efficacy of each of the treatment options separately for asymptomatic and symptomatic carotid artery disease. Since this is a single-center study and lacks control group(s), the authors of this study are aware that multicenter trial data and our institutions' single-center data are not directly comparable.

CONCLUSION

We found low rates of both early and late complications after CAS, especially in terms of clinical complication rates, which could suggest an all-around safety and efficiency of the method and the expertise of our center in performing CAS. Our results are similar to data shown in other studies that studied CAS effectiveness. By comparing our re-

sults with current international literature on both CAS and CEA efficiency, we intended to show that CAS is as valuable and a comparable method of treatment of carotid artery stenosis as CEA. In our results, we report that only hemodynamically significant stenosis has an impact on early outcome of CAS which may be due to the all-around low complication rates in our study.

CAS is a non-invasive method of treatment and has an all-around sparing effect on patients, but the emphasis is on proper patient selection. An individualized approach to each patient is needed when deciding which patients are suitable for CAS. Our results showed that it can be considered as efficient and safe treatment option for carotid artery stenosis as CEA in carefully selected patients. This result has however to be proven prospectively on the larger cohort of patients.

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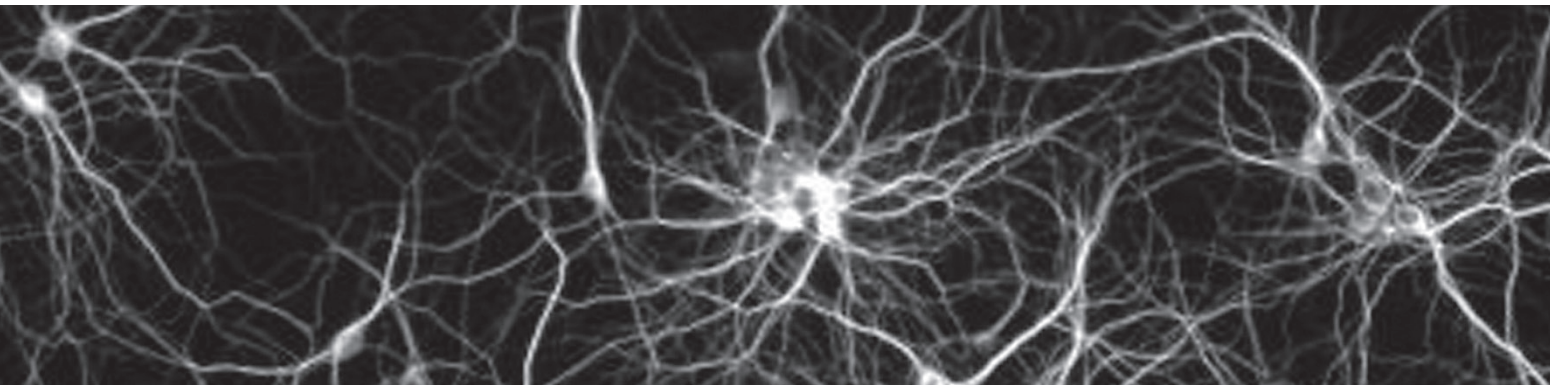

The quality of life in people with multiple sclerosis in Varaždin County

Tea Sokol[1], Dominik Piskač[2], Matija Hunjek[1], Spomenka Kiđemet-Piskač[1,3], Damir Poljak[3], Jurica Veronek[3,4], Marijana Neuberg[3]

ABSTRACT – *Background:* Multiple sclerosis (MS) is a chronic autoimmune disease that affects the central nervous system, causing damage to the myelin sheath and axons, which interferes with the normal conduction of nerve impulses. Symptoms, which can vary greatly from one individual to another, significantly affect the quality of life of those affected. *Methods:* The study was conducted from January to June 2023 on 46 patients with MS in Varaždin County, The Republic of Croatia, focusing on the challenges they face, the impact of their work capacity and education on quality of life, the impact of the disease itself on family planning, the impact of the disease on family relationships and satisfaction with social assistance services offered in the community. The questionnaire had a total of 22 questions, and completing the questionnaire was exclusively voluntary. *Results:* The results of our study clearly indicate the negative impact of MS on the quality of life of people with MS and a significant connection between education and the quality of life of people with MS. Highly educated participants in the study often reported better mental hygiene, which suggests that education can have a positive impact on aspects of mental health. The incidence of depression, anxiety and other emotional challenges is often lower among highly educated people. The disease also has a great impact on family planning. Also, there is still a significant presence of stigmatization of patients with MS, which is why they close themselves within the family circle, and there they most often seek help, which undermines their social integrity. *Conclusion:* Our study, as well as the research of other authors, serves as a basis for development of interventions that would improve social integration and the quality of life of people with MS.

Keywords: multiple sclerosis, quality of life, patient experience, quality improvement

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INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune disease that affects the central nervous system, causing damage to the myelin sheath and axons, which interferes with the normal conduction of nerve impulses. Symptoms of MS, which range from mild to severe, include numbness and other sensory phenomena, weakness of limbs, mood swings, memory problems, fatigue, sphincter disorders, sexual dysfunction, and numerous difficulties that interfere with patients' daily functioning and affect their private and professional lives, family planning, and the need for caregivers and/or personal assistants (1). According to the Croatian Institute of Public Health, there are 7024 people in Croatia registered with MS, and the disease significantly affects the quality of life of patients (2,3). Understanding symptoms and their impact on daily life is crucial for improving care, developing new treatment options, as well as improving the quality of life of patients.

RESPONDENTS AND RESEARCH METHODS

The study was conducted from January to June 2023 using a questionnaire that, in addition to demographic data, contained questions about the level of education, duration of the disease, quality of work and private life, the impact of disease progression on this quality of life, and satisfaction with social assistance services offered in the community. The questionnaire had a total of 22 questions, and completing the questionnaire was exclusively voluntary, after receiving approval from the Ethics Committee of the Varaždin General Hospital. Participants were informed about the study and its goals and signed an informed consent to participate in the study. The questionnaire was compiled by the first author of this paper, based on her experience working in the neurological department of the Varaždin General Hospital. The study aimed to examine the quality of life of people with MS, of whom there are over 200, according to the data from the Varaždin County Multiple Sclerosis Society and the Hospital Information System of the Varaždin General Hospital. Data analysis was done with Google Forms software which was also the method for conducting the questionnaire. This type of data collection method is common for members of MS society because it is often applied in various research, so participants had no difficulty using the Google Forms software. Answers from 46 participants diagnosed with MS provided the necessary data and could offer guidelines for further research and therapeutic approaches, with a focus on the needs and challenges faced by patients and the impact on their quality of life.

RESULTS

Of the 46 participants included, 71.7% were women, 28.3% were men. Most participants (30.4%) were between the ages of 31 and 40, while 28.3% were between the ages of 41 and 50, and only one participant was under the age of 20. The median age of the participants is 23.5 years while the standard deviation is 11 years (Fig. 1). The gender of participants is shown in Figure 2. When it came to the employment status of the participants, most of them (56.5%) had regular full-time employment. Twelve participants (26.1%) were retired, while 3 participants (6.5%) were on sick leave. One participant (2.2%) stated that he is permanently unable to work and one (2.2%) that he was employed part-time. Fifty percent of the respondents first learned about the diagnosis between the ages of 18 and 29. Another significant group was made up of 28.3% of the participants who learned about the diagnosis between the ages of 30 and 40, while a smaller number of respondents learned about the diagnosis at a slightly older age (over 41). When asked about the duration of the disease among the participants, the majority of respondents (39.1%) have been living with MS for between 1 and 5 years. This

Fig. 1. *Participants' age groups (median age is 23.5 years, the standard deviation is 11 years)*

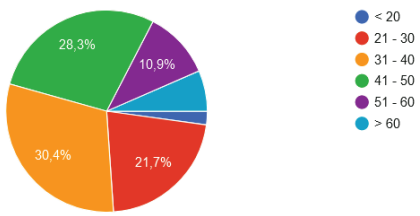
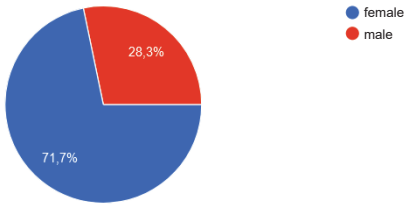


Fig. 2. *Participants' gender*



is followed by people who have been dealing with this disease for more than 10 years, while only a small percentage (2.2%) of those affected were diagnosed a few months ago. The largest number of participants in the study (63%) has a diagnosis of a relapsing form of the disease, 28.3% have a primary progressive form, while 8.7% of our participants have a secondary progressive form.

Participants were asked to rate their health status themselves, using a scale from 1 to 5, where a score of 1 indicated poor health, a score of 2 satisfactory health, a score of 3 good health, a score of 4 very good health and a score of 5 indicated excellent health. Analyzing the results, we can see that the mean score that the participants assigned to their health status was 3, which indicates an average perception of their health, as shown in Figure 3.

As part of the survey, participants were asked how the progression of the disease affects their daily lives, and this is shown in Figure 4.

The largest percentage of our respondents had secondary (high school) or higher education, as shown in Figure 5, which was important for understanding whether the level of education affects the patients.

The survey also examined how the progression of MS affects the participants' private and professional lives and whether they seek professional help. The answers to this question are diverse, which highlights the individual aspects of coping with the disease. As can be seen from Figure 6, most participants seek help from their families in coping with the challenges of the disease, and only a small number of sufferers communicate with strangers about their disease. The disease affects the professional and private lives of almost 20% of subjects.

The question was also whether patients needed the involvement of caregivers and/or personal assistants in performing daily activities. The results again show the diversity of needs among patients, i.e., that the periodic challenges of worsening disease related to relapses also significantly affect the need for additional help, as shown in Figure 7.

Fig. 3. *Mean rating given by participants' to their health status*

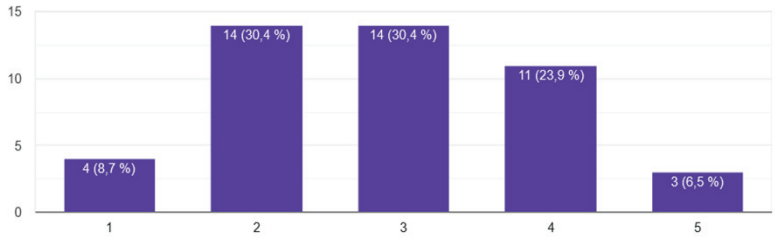


Fig. 4. *Impact of disease progression on daily life*

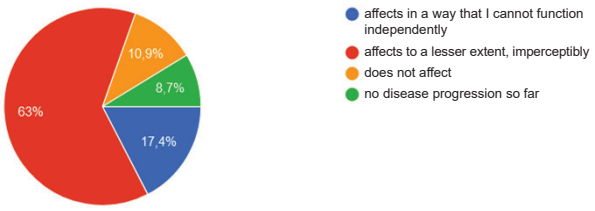


Fig. 5. *Participants' level of education*

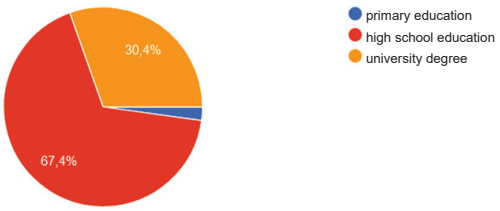


Fig. 6. *Illness impact on participants' private and business lives*

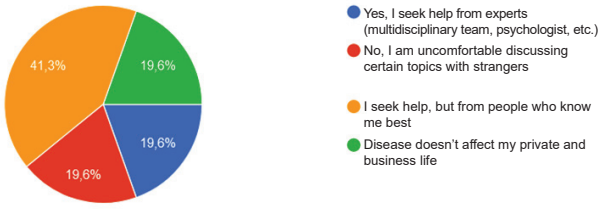


Fig. 7. *Illness impact on the need for caregivers and/or personal assistants*

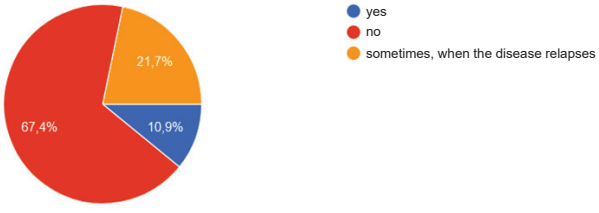


Figure 8: *Disease impact on finding employment for people with MS*

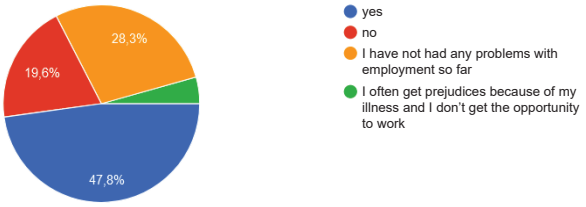


Fig. 9. *Impact of MS on family planning*

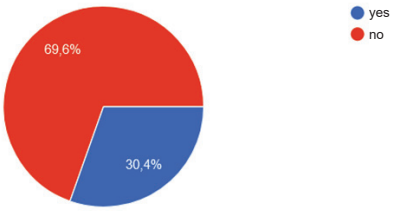
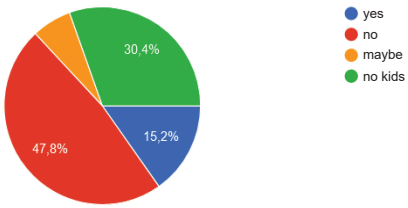


Fig. 10. *The impact of MS on family planning regarding the second or subsequent child*



People with disabilities, including those with MS, often face challenges when seeking employment. Sometimes, the symptoms of this disease are invisible, which further complicates the situation. For the purpose of the research, participants were asked about their perception of the difficulty of finding employment compared to people without such health challenges, and the results are shown in Figure 8. The answers suggest the existence of certain obstacles and challenges when seeking employment, although this varies between individuals, which certainly has to do with the clinical manifestation of the disease in the individual, but also with the still present prejudices about the ability of a person with MS to perform jobs and emphasize the need to break down prejudices and create an environment that will provide equal opportunity for all.

As part of the research, the impact of multiple sclerosis on family planning and pregnancy among participants was analyzed. The analysis shows that the majority of respondents believe that MS did not significantly affect their pregnancy plans. On the other hand, the vast majority of people with MS would not decide to have a second or subsequent child. The same is shown in Figure 9 and 10.

DISCUSSION

Quality of life is a complex and subjective concept that describes the overall experience and perception of life of an individual or a community. There is no single definition, but it includes various elements such as physical health, mental well-being, emotional stability, social relationships, economic security, environmental conditions and many other factors. Quality of life is measured according to individual perceptions and values and can vary between different people and cultures. This concept often serves as a basis for research and analysis of how different factors influence the experience and satisfaction with life. Measuring the quality of life of people with MS has become an inevitable step in many studies in the last twenty years (4,5).

MS has a significant negative impact on quality of life (6). The results of our study clearly indicate the negative impact of MS on the quality of life of people with MS. Although the majority of participants, 63% of them, believe that the progression of the disease affects their lives to a lesser extent, this does not mean that MS does not have a negative impact on their everyday lives. For many, MS can present challenges and obstacles that are often not visible from the outside, which can result in a feeling of less control over their own lives. At the same time, 17.4% of participants feel that the progression of MS has a significant impact on them, to the point that it makes it difficult to function independently. While some people manage to maintain a relatively stable state and feel less of an impact of the disease on their quality of life, others face challenges that can significantly disrupt their daily lives. The disease also has a great impact on family planning.

The results of the study indicate a significant connection between education and the quality of life of people with MS. Highly educated participants in the study often reported better mental hygiene, which suggests that education can have a positive impact on aspects of mental health. These results have a deeper meaning when combined with the fact that highly educated individuals are often better able to cope with the challenges that MS can pose. The incidence of depression, anxiety and other emotional challenges is often lower among highly educated people. This may be a consequence of their ability to better understand the disease,

which allows them to better prepare for and face its challenges. It is important to note that highly educated participants often showed a greater tendency to seek out and use educational resources about MS. Education plays a significant role in improving the quality of life of people with MS. People who understand their disease better are often better prepared to manage it and make decisions about their treatment (7).

What we must especially emphasize as the importance of this research is the still significant presence of stigmatization of patients, which is why they close themselves within the family circle, and there they most often seek help, which undermines their social integrity, and this is in line with the results of other authors. We emphasize the work of Persson and colleagues, who examine the context of social relationships, support, feelings of isolation, and the ways in which MS shapes interactions and social participation (8). The results of the authors' research suggest that MS can significantly affect the social network and participation of patients with an emphasis on the need for support and understanding of the environment, which has already been described in the works of Mikul *et al.* and Koch-Henriksen *et al.* (9,10). The study's limitations were the use of Google Forms, which may lead to selection bias, as individuals with lower levels of digital literacy may be excluded. Our research, as well as the research of the aforementioned authors, serve as a basis for the development of interventions that would improve social integration and the quality of life of people with MS.

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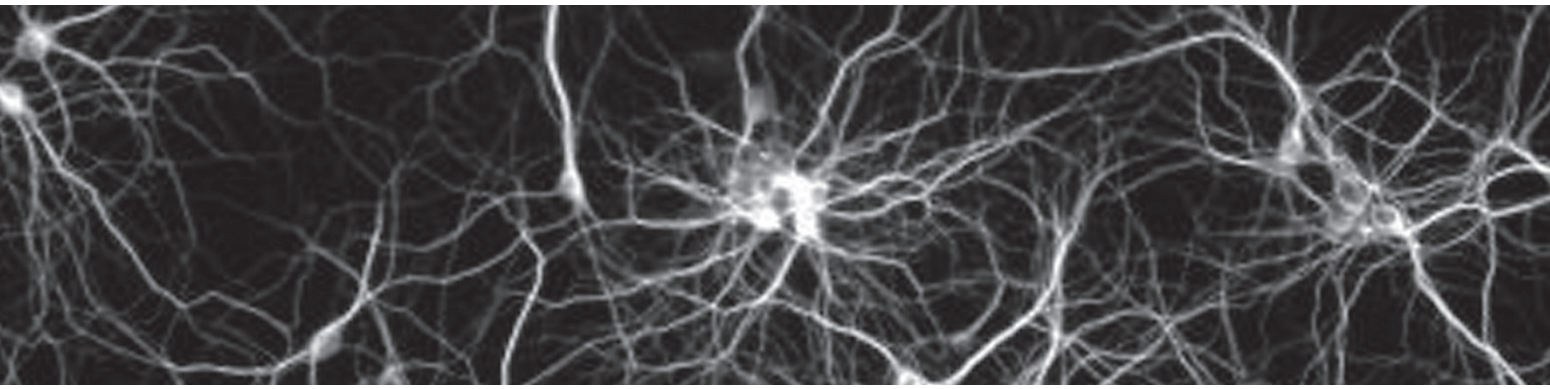

Association of alemtuzumab treatment with lymphoma development in a patient with relapsing-remitting multiple sclerosis

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ABSTRACT – *Objectives:* Alemtuzumab, a humanized monoclonal antibody targeting CD52, has shown high efficacy in treating relapsing-remitting multiple sclerosis (RRMS), especially in patients with active disease who do not respond to other therapies. However, its use carries significant adverse effects, including a possible risk of malignancy. *Case description:* This report presents the case of a 64-year-old female with RRMS who developed diffuse large B-cell lymphoma (DLBCL) following alemtuzumab treatment. The patient received alemtuzumab as part of the CAMMS clinical trial, achieving long-term remission of RRMS. *Results:* However, in 2020, she developed symptoms that led to a DLBCL diagnosis. Despite numerous complications during treatment, complete remission from lymphoma was achieved following R-CHOP chemotherapy. *Conclusion:* This case highlights the need for vigilant monitoring of patients treated with alemtuzumab, particularly for hematologic abnormalities and potential malignancies. While the link between alemtuzumab and lymphoma remains speculative, this report contributes to a better understanding of the long-term risks associated with alemtuzumab therapy and underscores the necessity for further research.

Keywords: alemtuzumab, diffuse large B-cell lymphoma

INTRODUCTION

Treatment of relapsing-remitting multiple sclerosis (RRMS) aims to reduce relapse frequency, slow disease progression, and minimize neurological disability. Alemtuzumab, a humanized monoclonal antibody targeting the CD52 glycoprotein on lymphocytes, has shown high efficacy in RRMS, especially in patients with active disease unresponsive to other therapies (e.g., IFN-β1a) (1). Despite

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its benefits, alemtuzumab carries significant risks. Sold under the brand names Lemtrada for RRMS and Campath for B-cell chronic lymphocytic leukemia (B-CLL), dosing and frequency differ between indications.

This case report describes a 64-year-old person with RRMS who developed DLBCL following treatment with alemtuzumab. This raises a paradoxical question: Could a drug commonly used to treat lymphoma (in higher doses for B-CLL than for RRMS) actually contribute to the development of lymphoma?

CASE REPORT

The patient, born in 1961, was diagnosed with RRMS in 2003. From 2008 to 2012, she participated in the CAMMS trial (Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis), receiving four cycles of alemtuzumab. During the follow-up study TOPAZ (2015–2020), her neurological status stabilized without somatic complications, and her EDSS was reported to be 3.0. The patient's comorbidities included hypertension, chronic gastritis, and severe radiculopathy. Her surgical history encompassed tonsillectomy, sinus polypectomy, appendectomy, breast fibroma excision, cervical intraepithelial neoplasia (CIN) treatment, and two surgeries for lumbar radiculopathy. The patient experienced complex family relationships and challenging living conditions, alongside a history of long-term smoking (30 pack-years), and had previously attempted suicide through drug overdose in 2009, suggesting underlying psychological instability.

In early 2020, she developed diffuse abdominal pain, nausea, vomiting, weight loss, fatigue, and night sweats (without fever). MSCT revealed widespread lymphadenopathy (paraaortic, paratracheal, subcarinal, bilateral axillary, and left supraclavicular, with a conglomeration of enlarged lymph nodes extending from the diaphragm to the aortic bifurcation) and splenic infiltration, suggesting non-Hodgkin lymphoma. A lymph node biopsy confirmed stage IV B diffuse large B-cell lymphoma (DLBCL) with bone marrow involvement. Treatment with R-CHOP began on April 23, 2020. The first cycle was complicated by fever and elevated inflammatory parameters. After four cycles, imaging showed significant partial regression of lymphadenopathy. Treatment continued with additional complications. After the fifth cycle, the patient developed stomatitis; the sixth cycle was postponed due to pancytopenia, and the seventh cycle was also delayed because of leukopenia and thrombocytopenia. The last cycle (eighth) was administered on October 16, 2020. Despite the numerous complications, a significant therapeutic response and complete remission of the disease were recorded.

From 2022 onward, recurrent symptoms (fatigue, night sweats, loss of appetite, and lymphadenopathy in the neck, groin, and armpits) raised suspicion of relapse; however, cytology and histology from the suspected lymph nodes were negative. Throughout lymphoma treatment, her neurological status remained stable, with no MS relapses or changes in EDSS, which remained at 3.0.

DISCUSSION

Alemtuzumab is a high-efficacy drug used for the treatment of RRMS, particularly in patients with active disease. This humanized monoclonal antibody targets CD52, a glycoprotein found on the cell surface at high concentrations on T (CD3+) and B lymphocytes (CD19+), and at lower concentrations on NK cells, monocytes, and macrophages. Alemtuzumab exerts its effects through antibody-dependent cytolysis and complement-mediated lysis after primarily binding to T and B lymphocytes. This mechanism leads to rapid and long-lasting depletion of CD52-positive cells, followed by slow repopulation from unaffected hematopoietic precursor cells (1). Despite its high efficacy, alemtuzumab is associated with significant risks. Some of the most important and common adverse events linked to alemtuzumab administration include infusion-related reactions (>90%), primarily respiratory infections (66-77%), thyroid disorders (29.6%), hematological abnormalities such as hemolytic anemia, ITP, pancytopenia, agranulocytosis (1-3%), and glomerulonephritis (0.3%) (1).

Clinical trials have reported a low incidence of malignancies in patients treated with alemtuzumab. Lymphoproliferative malignancies, including lymphoma, Castleman's disease, and Burkitt's lymphoma that are unrelated to Epstein-Barr virus, occurred in control groups at comparable rates. In the CAMMS223 study, three cases of cancer were reported after treatment with alemtuzumab: breast cancer, Burkitt's lymphoma, and cervical cancer, with an onset of 22 to 64 months after the drug was administered. Overall, across all clinical studies, 29 of 1,486 patients developed malignancies (2). An isolated case of CNS atypical T-cell lymphoprolif-

erative disease related to alemtuzumab therapy has also been reported (3). Additionally, another case of diffuse large B-cell lymphoma (DLBCL), following alemtuzumab therapy for T-cell prolymphocytic leukemia (T-PLL), has been described. This case highlights the possible negative effects of T-cell depletion, which can lead to immunosuppression and reactivate latent EBV infection in the patient (5).

Along with alemtuzumab being a possible cause of hematological malignancies, multiple sclerosis is also considered; however, several studies, including one by Fallah *et al.*, have shown that multiple sclerosis, as a fundamental autoimmune disease, does not elevate the risk of malignant diseases, unlike other autoimmune disorders (4). Although there have been descriptions of lymphoproliferative disorders following the use of alemtuzumab, we have not encountered any findings on the occurrence of DLBCL in the context of this treatment.

It is somewhat paradoxical to suspect that alemtuzumab is responsible for the development of lymphoma, as it is simultaneously listed as a treatment for patients with B-CLL. However, the strong and long-term immunosuppression caused by alemtuzumab should be considered. We hypothesize that weakened immune surveillance could have contributed to the occurrence of a secondary lymphoproliferative disorder in our case. Thus, while alemtuzumab is indicated in B-CLL and has an antitumor effect on existing lymphoproliferative cells, its non-specific lymphocyte depletion may impair the body's ability to recognize and eliminate newly formed malignantly transformed clones over time.

Despite the risks associated with alemtuzumab therapy, the therapeutic effect of the drug in this case was significant. The patient exhibited clinical and radiological improvement, achieving complete stabilization of RRMS symptoms without a relapse for over a decade. MR imaging revealed no new lesions, and the EDSS scale (Expanded Disability Status Scale) remained unchanged, confirming the high efficacy of alemtuzumab in disease management. Although the patient later developed DLBCL, treatment with the R-CHOP protocol also yielded excellent results, leading to complete lymphoma remission after eight cycles of therapy.

The case highlights the importance of continuously monitoring patients treated with alemtuzumab, particularly for the detection of hematological abnormalities. Regular monitoring of blood counts, new symptoms, and lymph node status is essential for the early detection of potential malignancies. It is important to consider that distinguishing whether some symptoms are due to the natural progression of RRMS, side effects of therapy, or unintentional malignancies can be difficult. This case also underscores the need for an individualized risk-benefit analysis when selecting therapy for RRMS, while also taking potential long-term complications into account. Although a direct causal link between alemtuzumab and lymphoma remains speculative, this case contributes to the growing body of data regarding possible risks. Further research is needed to clarify the association between alemtuzumab, RRMS, and hematological malignancies.

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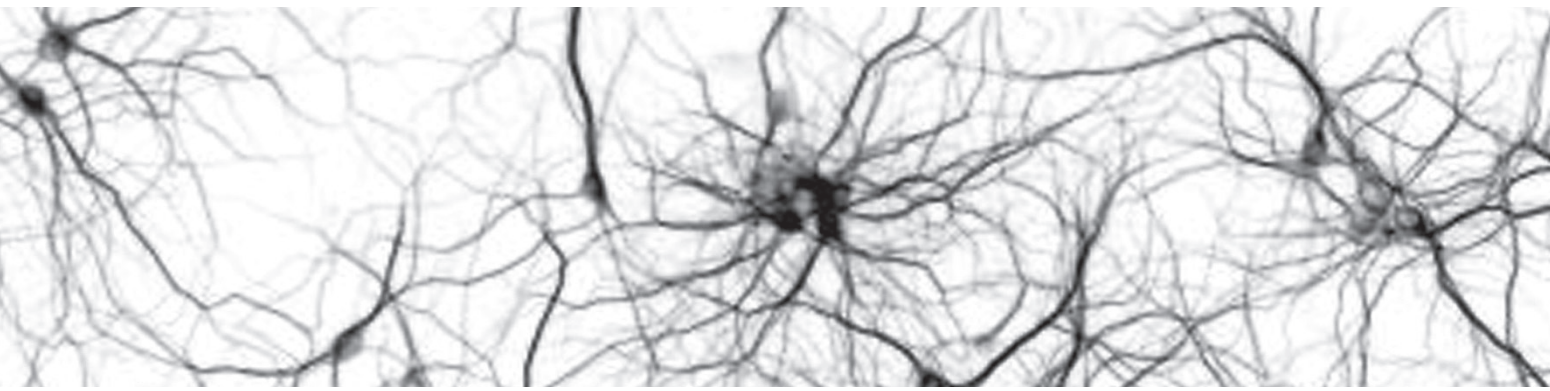

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