ORIGINAL ARTICLE

Inflammatory lesions in the paranasal sinuses in patients with ischemic stroke who underwent mechanical thrombectomy

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KEY WORDS

inflammation, rhinosinusitis, stroke, thrombectomy

EDITORIAL

by Lin, Cheng, and Yang, see p. 322

ABSTRACT

INTRODUCTION Chronic rhinosinusitis is one of the most widespread chronic diseases in the world, whereas stroke is the leading cause of death and disability. There are numerous reports on the relationship between chronic inflammatory diseases and cardio-cerebrovascular diseases.

OBJECTIVES The study aimed to assess whether inflammatory lesions in the sinuses can be a risk factor for stroke, similar to other known risk factors such as arterial hypertension, atrial fibrillation, atherosclerosis, diabetes, or cigarette smoking.

PATIENTS AND METHODS We analyzed the results of head computed tomography performed in 163 patients with ischemic stroke (79 men) at a mean (SD) age of 68.5 (12.7) years who were deemed eligible for mechanical thrombectomy. The control group included 75 patients (31 men) with neurological diseases of nonvascular origin.

RESULTS Among patients with stroke, inflammatory lesions in the sinuses were found in 95 individuals (58.3%), with a frequency comparable to that of atrial fibrillation (77 [47.2%]). Chronic rhinosinusitis occurred more often than diabetes (33 [20.2%]; $P < 0.001$) and self-reported nicotinism (18 [11%]; $P < 0.001$), yet less frequently than arterial hypertension and generalized atherosclerosis (124 [76.1%]; $P < 0.001$ and 116 [71.2%]; $P = 0.02$, respectively). Inflammatory sinus lesions of moderate or high severity were more often observed in patients with stroke than in the control group and they mainly involved the ethmoid sinuses.

CONCLUSIONS Moderate-to-severe inflammatory lesions indicating chronic rhinosinusitis are common in patients with stroke, which suggests the role of local inflammation in inducing acute cerebral ischemia.

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Received: November 13, 2020.
Revision accepted: February 24, 2021.
Published online: February 25, 2021.
Pol Arch Intern Med. 2021; 131 (4): 326-331
doi:10.20452/pamw.15848

INTRODUCTION Chronic rhinosinusitis (CRS) is one of the most widespread chronic diseases in the world, affecting 11% of Europe's population[1,2] and 12.5% of the United States population.[3,4] There are known complications of CRS resulting from the anatomical proximity of the sinuses and the brain, such as brain abscess, subdural empyema, cranial nerve palsy, and meningitis. Chronic rhinosinusitis may lead to cavernous sinus and jugular vein thrombosis, as well as mycotic aneurysm.[5-10] Furthermore, a relationship between chronic inflammatory diseases and cardio-cerebrovascular diseases has been noted.[11] Previous cohort studies revealed that patients with CRS were at higher risk of acute myocardial infarction and stroke.[12-16]

The aim of our study was to assess whether inflammatory lesions in the sinuses may represent a risk factor for ischemic stroke, similar to that posed by arterial hypertension (AH), atrial fibrillation (AF), atherosclerosis, diabetes, or cigarette smoking. We compared the computed tomography (CT) scans of paranasal sinuses in patients deemed eligible for mechanical thrombectomy

WHAT'S NEW?

Numerous researchers have emphasized the association of chronic inflammatory diseases and cardio-cerebrovascular diseases. In previous reports (retrospective cohort studies) on the relationship between chronic rhinosinusitis and the occurrence of stroke (ischemic or hemorrhagic), rhinosinusitis was diagnosed based on *International Classification of Diseases, Tenth Revision* (*ICD-10*) codes. In our study, inflammatory lesions in the sinuses were identified by computed tomography of the head, performed in the ultra-acute disease period (up to 6 hours following the first stroke symptoms). Our findings show that inflammatory lesions in the sinus were more common than diabetes and nicotinism and as common as atrial fibrillation in patients with ischemic stroke who underwent thrombectomy. A large labyrinth of anterior and posterior ethmoid cells lined with the mucosa and the presence of arteries might favor a faster transport of inflammatory mediators produced in the sinus.

due to ischemic stroke and those with central nervous system diseases of nonvascular origin. Subsequently, we analyzed the extent of inflammation in individual paranasal sinuses in both groups in order to assess which patients developed the most severe inflammatory lesions.

PATIENTS AND METHODS This single-center, retrospective, observational, case-control study included patients referred to the Department of Neurology of the Leszek Giec Upper Silesian Medical Centre of the Silesian Medical University in Katowice-Ochojec in 2019. Eligible patients were those with ischemic stroke in whom mechanical thrombectomy was indicated according to the 2018 guidelines for the management of acute ischemic stroke.[17] Patients in whom diagnostic workup confirmed the presence of embolic material in cerebral vessels were selected for analysis.

The control group consisted of patients with neurological diseases of nonvascular origin (*International Classification of Diseases, Tenth Revision* [*ICD-10*] codes: G20, G30, G40, C71, and G96). Patients with vascular brain injury (Fazekas score ≥2) and those treated with thrombolytic or endovascular therapy within at least 3 months prior to study enrollment were not included. During hospital stay, patients underwent several imaging examinations of the head (tomography, CT angiography of the cerebral vessels, and nuclear magnetic resonance imaging) to diagnose the underlying disease. Tomography also enabled us to evaluate the extent of inflammation within the paranasal sinuses.

In both study groups, we assessed the extent of inflammation in the paranasal sinuses based on a CT scan performed on the first day of hospitalization using Optima CT 540 (GE Healthcare, Chicago, Illinois, United States) without contrast enhancement.

In the stroke group, CT was performed on the first day of hospitalization, and in the control group, within the first 3 days of hospital stay, to exclude the possibility of hospital-acquired sinusitis.

The sinuses were examined in 3 planes. Inflammatory lesions were assessed using the Lund–Mackay score (the degree of opacification in the maxillary, anterior and posterior ethmoid, frontal, and sphenoid sinuses as well as the obstruction of the ostiomeatal complexes were evaluated [on both sides]) on a 0–2 scale [a maximum of 24 points]).[18] Depending on the number of points assigned, the following categories of CRS stages were distinguished: 0—normal, 1 to 3—mild, 4 to 10—moderate, and >10—severe. In this study, the term CRS refers only to inflammatory lesions in the sinuses apparent on a head CT scan, and not to data on clinical complaints and treatment, as suggested by the EPOS.[18,19]

In both study groups, patients' history included information on sex, age, comorbidities such as AH, diabetes, atherosclerosis (defined as symptomatic ischemic heart disease during the last 6 months and / or carotid stenosis, and / or lower limb ischemia), AF, and smoking status. C-reactive protein levels were also measured in all patients.

Exclusion criteria included medical history suggesting sinus complaints and their possible treatment within the last 2 months, acute infection, thrombolytic or endovascular therapy within at least 3 months prior to study enrollment, and vascular brain injury (Fazekas score ≥2) at inclusion.

Statistical analysis Study results were expressed as absolute numbers and percentages for frequency, mean (SD) for age, or median values with interquartile ranges for the Lund–Mackay score. The nonparametric Mann–Whitney rank sum test was used. Frequencies were compared using the *z* test for proportions. Multiple regression analysis was conducted with age, sex, AF occurrence, AH, diabetes, and atherosclerosis to determine the association with the Lund–Mackay score in both study groups. All analyses were performed using the Statistica 13.3 software package (StatSoft, Kraków, Poland). A *P* value less than 0.05 was considered significant.

Ethics Ethics committee approval was not required for this study, as the adopted approach did not differ from the applied treatment standards.

RESULTS The study included 165 patients with ischemic stroke. Two patients in whom CT was performed in another center were excluded from analysis. Eventually, data of 163 patients (79 men and 84 women) were analyzed. The mean (SD) age of patients was 68.5 (12.7) years. The control group consisted of 75 patients, including 31 men and 44 women, at a mean (SD) age of 55.4 (22.4) years.

Chronic rhinosinusitis in the stroke and control groups Inflammatory lesions in the sinuses were found in 95 patients (58.3%) from the stroke group, with the following degrees of severity: mild in 35 patients (36%), moderate in 44 (46%), and

TABLE 1 Occurrence of inflammatory lesions in the sinuses by severity

Parameter		Patients with stroke (n = 163)	Controls (n = 75)	*P* value
CRS, Lund–Mackay score >1		95 (58.3)	34 (45.3)	0.06
Lund–Mackay score, median, (IQR; total range)		2 (0–5; 0–18)	0 (0–2; 0–7)	<0.001
Lesion severity	Mild (Lund–Mackay score, 1–3)	35 (37)	24 (71)	<0.001
	Moderate (Lund–Mackay score, 4–10)	44 (46)	10 (29)	0.08
	High (Lund–Mackay score >10)	16 (17)	0 (0)	NA
CRS, Lund–Mackay score >3		60 (36.8)	10 (13.3)	<0.001

Data are presented as number (percentage) of patients unless otherwise indicated.

Abbreviations: CRS, chronic rhinosinusitis; IQR, interquartile range; NA, not applicable

TABLE 2 Clinical characteristics of the study patients

Parameter		Patients with stroke (n = 163)	Controls (n = 75)	*P* value
Age, y, mean (SD)		68.5 (12.7)	55.4 (22.4)	<0.001
Sex	Male	79 (48.5)	31 (41.3)	0.3
	Female	84 (51.5)	44 (58.7)	
Atrial fibrillation		77 (47.2)	6 (8)	<0.001
Arterial hypertension		124 (76.1)	34 (45.3)	<0.001
Diabetes		33 (20.2)	10 (13.3)	0.2
Atherosclerosis		116 (71.2)	15 (20)	<0.001
Smoking status		18 (11)	17 (22.6)	0.02
CRP, mg/l, median (IQR; total range)		9.5 (5–17.5; 5–163)	10.3 (5–15.8; 5–91.6)	0.05

Data are presented as number (percentage) of patients unless otherwise indicated.

Abbreviations: CRP, C-reactive protein; others, see TABLE 1

high in 16 (17%). In the control group, such lesions were detected in 34 patients (45.3%). Those were mild (Lund–Mackay score <4) in the majority of patients (24 [71%]) and moderate in 10 (29%).

The comparison of stroke and control groups showed that inflammatory lesions in the sinuses were more common in the former group, but this was nonsignificant (95 [58.3%] vs 34 [45.3%]; $P = 0.06$). When patients with low Lund–Mackay scores, that is, between 0 and 3, were regarded as patients without CRS, CRS defined in this way occurred more frequently in the stroke group than in controls (60 [36.8%] vs 10 [13.3%]; $P < 0.001$).

The severity of rhinosinusitis assessed by the Lund–Mackay score was higher in patients with stroke than in the control group (median [interquartile range], 2 [0–5] vs 0 [0–2]; $P = 0.001$), and more patients with stroke had severe inflammatory lesions in the sinuses (Lund–Mackay score >10; 16 [17%] vs 0) (TABLE 1).

Coexistence of other diseases in the study groups In patients who underwent mechanical thrombectomy for ischemic stroke, CRS was diagnosed in 95 individuals (58.3%), at a frequency similar to that of AF (77 [47.2%]). Chronic rhinosinusitis occurred more frequently than diabetes (33 [20.2%]; $P < 0.001$) and the reported history of smoking (18 [11%]; $P < 0.001$), yet less frequently than AH and atherosclerosis (124 [76.1%]; $P < 0.001$ and 116 [71.2%]; $P = 0.02$, respectively) (TABLE 2).

In the control group, CRS was observed in 34 patients (45.3%), more often than AF (6 [8%]; $P < 0.001$), diabetes (10 [13.3%]; $P < 0.001$), atherosclerosis (15 [20%]; $P < 0.001$), and nicotinism (17 [22.6%]; $P = 0.005$), and as often as AH (34 [45.3%]; $P > 0.99$) (TABLE 2).

C-reactive protein levels were similar in both groups. Atrial fibrillation, AH, and generalized atherosclerosis were more frequent in patients with stroke compared with controls, whereas diabetes occurred at similar frequency. The history of smoking was more often reported in the control group than in patients with stroke (TABLE 2).

Multiple regression analysis including age, sex, AF occurrence, AH, diabetes, and atherosclerosis showed that the severity of CRS was associated only with the male sex in the stroke group ($P = 0.04$) and none of the analyzed factors in the control group. In the stroke group, there were more male patients (58 [73%]) with CRS than without (21 [27%]; $P < 0.001$).

Assessment of the extent of inflammatory lesions in individual sinuses This study also aimed to assess which sinuses were mainly affected by inflammation, with the Lund–Mackay score of more than 3 points. We found that only the ethmoid sinuses were affected by inflammation corresponding with that score. Inflammatory lesions with the Lund–Mackay score of fewer than 3 points were equally common in all evaluated sinuses (TABLE 3).

In the control group, the maxillary and ethmoid sinuses were most often affected, whereas the extent of inflammation over 3 points according to the Lund–Mackay scale was observed in the ethmoid sinuses only (TABLE 3).

DISCUSSION

The objective of this study was to assess whether chronic inflammation in the paranasal sinuses could be considered a risk factor for stroke in patients with acute ischemic stroke. The study was conducted in a fairly homogeneous group of patients with ischemic stroke—all of them underwent reperfusion therapy, mechanical thrombectomy. The presence of inflammatory lesions in the sinuses was determined based on CT of the head performed at the ultra-acute stage of the disease (up to 6 hours after the first stroke symptoms). Inflammatory sinus lesions detected by head CT provided an objective confirmation of chronic inflammation of varying severity, which could not be related to hospital-acquired infection, as the examination was performed on the first day of hospitalization. No lesions in the sinuses suggesting malignancy (bone infiltration and destruction, spread beyond the sinuses) were found. Patients hospitalized for reasons

TABLE 3 Inflammatory lesions in various types of sinuses on computed tomography

Parameter		Sinus							
		Ethmoid		Sphenoid		Frontal		Maxillary	
		Stroke group (n = 95)	Controls (n = 34)	Stroke group (n = 95)	Controls (n = 34)	Stroke group (n = 95)	Controls (n = 34)	Stroke group (n = 95)	Controls (n = 34)
Severity of inflammatory lesions in the sinuses according to the Lund–Mackay score, points	6	4	1	0	0	0	0	0	0
	5	2	0	0	0	0	0	0	0
	4	22	4	0	0	0	0	0	0
	3	1	1	1	0	0	0	2	0
	2	26	9	19	1	28	2	25	7
	1	16	0	17	8	16	8	28	13
Patients with lesions of any severity in particular sinuses, n (%)		71 (74.7)[a]	15 (44.1)	37 (38.9)	9 (26.5)	44 (46.3)	10 (29.4)	55 (58)	20 (58.8)
P value for comparison between the groups		0.001		0.19		0.08		0.93	
Patients with lesions in particular sinuses with a Lund–Mackay score of 4–6, n (%) of all patients with lesions in a particular sinus		28 (39.4)	5 (33.3)	0	0	0	0	0	0
Patients with lesions in particular sinuses with a Lund–Mackay score of 1 to 3, n (%) of all patients with lesions in a particular sinus		43 (60.6)	10 (66.6)	37 (100)	9 (100)	44 (100)	10 (100)	55 (100)	20 (100)

a $P < 0.001$ for ethmoid vs sphenoid sinuses; $P = 0.001$ for ethmoid vs frontal sinuses; $P = 0.01$ for ethmoid vs maxillary sinuses in the stroke group

other than ischemic stroke, who also underwent head CT on the first hospitalization days as part of the diagnostic workup, constituted the control group.

Our study showed that in patients with ischemic stroke who underwent thrombectomy, inflammatory lesions in the sinuses were more frequent than diabetes and nicotinism, and as common as AF. Atrial fibrillation and nicotinism are recognized significant risk factors for stroke. Lesions suggestive of CRS were less frequent in patients with stroke than AH and atherosclerosis. A similar frequency of CRS was demonstrated in both stroke and control groups ($P = 0.06$). Inflammatory sinus lesions with a Lund–Mackay score exceeding 3 were more often detected in patients with stroke. Inflammatory lesions in the sinuses with a score of 1 to 3 usually do not have clinical relevance. They are often small and unilateral, which is why it was deemed reasonable to omit this group of patients when comparing the occurrence of CRS in the study population.

In patients with stroke, inflammation most often involved the surrounding sinuses, the so-called ostiomeatal complex, that is, ethmoid, frontal, and maxillary sinuses. Inflammation of greatest severity (Lund–Mackay score >3) was observed in the ethmoid sinuses. The ethmoid sinuses made up of multiple minor cells lined with mucosa have a large surface relative to their volume. These are the only sinuses that are vascularized (anterior and posterior ethmoid artery), often without a bone canal, which leads to direct contact with the mucosa altered by inflammation. It may facilitate the transport of inflammatory mediators in the vessels. Anterior ethmoid cells are contiguous with nasal structures and communicate through an important anatomical region: the ostiomeatal complex. This area is of key importance for the normal functioning of the anterior paranasal sinuses. When the ostiomeatal complex is narrowed or occluded, the ethmoid sinuses can easily become diseased, resulting in a higher incidence of acute and chronic rhinosinusitis.[20]

Of note, CRS was much more common in both study groups than in the general population (5%–12%).[18] When examining the incidence of CRS in the Dutch population, Dietz de Loos et al[21] stated that 12.8% of study participants had epidemiologically (symptom-) based CRS, and 23% of them had a Lund–Mackay score of 4 or greater. The prevalence of clinically (imaging-) based CRS was 3% or 6.4%, depending on the cutoff point. In patients with abnormalities on imaging (Lund–Mackay score >4), only 21% had epidemiologically based CRS.

In our study, CRS was diagnosed based on inflammatory lesions apparent on sinus imaging. The lack of data on the history of sinus complaints and treatment in accordance with the EPOS 2020 guidelines limited our study.[19] There were no results of subjective tests, such as the visual analog scale[22] or Sino-Nasal Outcome Test 22,[23] or accurate data on inhalation allergy, bronchial asthma, and hypersensitivity to nonsteroidal anti-inflammatory drugs.

Some studies reported that patients with chronic inflammatory diseases are at higher risk of coronary artery disease, peripheral vascular disease, cardiomyopathy, and stroke.[24,25] Inflammation also promotes the development of atherosclerosis. The effects of chronic inflammatory diseases

such as rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, and psoriasis on the cardiovascular system are known.[26-28] The inflammatory cytokines involved in CRS, such as C-reactive protein and interleukin 1 or interleukin 17, have also been speculated to play a role in the development of stroke.[29,30] Interleukin 1 may result in perivascular inflammation and progression of internal carotid artery thrombosis. Interleukin 17, particularly in combination with tumor necrosis factor α, has a proinflammatory, procoagulant, and prothrombotic effect on blood vessels.[31] The activity of proinflammatory cytokines causes endotheliopathy, which leads to the adverse modulation of cerebral flow and nerve tissue perfusion parameters. Thrombi, aneurysms, and wall rupture accompanied by local hemorrhage occur at the diseased vessel wall.

Platelets can be directly activated by bacterial antigens or activated leukocytes.[32] Bacterial lipopolysaccharides (acute infection with gram-negative bacteria) may induce stroke in rats with existing risk factors (old age, AH, and diabetes).[33] Of note, rich bacterial flora is present in the sinuses, and gram-negative bacteria are more common in patients over 65 years of age, which was observed in our previous studies.[34] In this population, comorbidities such as AH and diabetes occur more frequently. In our study, larger inflammatory lesions in the sinuses were observed in older patients with stroke, whereas Lee et al[15] demonstrated that the risk of stroke was greater in patients with CRS under 60 years of age.

Previous reports (retrospective cohort studies) on the relationship between CRS and the occurrence of stroke (ischemic or hemorrhagic) were carried out following a different methodological approach.[13,15,35] Rhinosinusitis was diagnosed based on *ICD-10* codes. Objective imaging findings or subjective scores for the assessment of inflammation were not analyzed. Nevertheless, the results of such analyses confirmed that CRS is a relevant risk factor for stroke.

Patients diagnosed with CRS often use drugs that reduce nasal congestion, which affects blood pressure and heart rate and can further contribute to the onset of stroke. In addition, the frequent use of systemic and local steroids is also significant.[36] In epidemiological studies, a strong relationship was found between cigarette smoking and CRS.[37-40] Smoking also represents a crucial risk factor for stroke, dependent on the number of cigarettes smoked per day, and increases mortality by around 15%.[40,41] In our studies, nicotinism was less common than inflammatory lesions in the sinuses.

Our study on the type of sinuses affected by the disease have suggested that special attention should be paid to abnormalities within the ethmoid sinuses. A relatively large labyrinth of anterior and posterior ethmoid cells lined with mucosa along with the presence of arterial vessels might promote a faster transport of inflammation-promoting mediators in that region.

Conclusions Moderate and severe chronic inflammatory lesions in the sinuses, especially in the ethmoid sinuses, are commonly seen in patients with stroke, which highlights the role of local inflammation in inducing acute cerebral ischemia. Our findings justify the recommendation to pay particular attention to paranasal sinuses in patients who have sustained or are at risk of ischemic stroke. When moderate or severe CRS is diagnosed in those patients, high-dose medical therapy or interventional treatment should be initiated as early as possible to prevent stroke and related complications. In the future, further studies should be carried out to assess the potential impact of CRS on the course of the acute phase of stroke, the effect of therapy, and the degree of poststroke disability.

ARTICLE INFORMATION

CONTRIBUTION STATEMENT GS-M conceived the concept of the study. GS-M and AL-B contributed to study design. All authors were involved in data collection. GS-M, JG, and MN-U analyzed the data and edited the final version of the manuscript. All authors approved the final version of the manuscript.

CONFLICT OF INTEREST None declared.

HOW TO CITE Stryjewska-Makuch G, Glück J, Niemiec-Urbańczyk M, et al. Inflammatory lesions in the paranasal sinuses in patients with ischemic stroke who underwent mechanical thrombectomy. Pol Arch Intern Med. 2021; 131: 326-331. doi:10.20452/pamw.15848

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