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Authors: Grażyna Stryjewska-Makuch, Joanna Glück, Marcelina Niemiec-Urbańczyk, Maria Humeniuk-arusiewicz, Bogdan Kolebacz, Anetta Lasek-Bal

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Paranasal sinus inflammatory changes in patients with ischemic stroke who underwent mechanical thrombectomy

Short title: Paranasal sinus inflammatory changes in patients with ischemic stroke

Authors: Grażyna Stryjewska-Makuch¹, Joanna Glück², Marcelina Niemiec-Urbańczyk¹, Maria Humeniuk-ARasiewicz¹, Bogdan Kolebacz¹, Anetta Lasek-Bal³

¹ Department of Laryngology and Laryngological Oncology, Leszek Giec Upper-Silesian Medical Centre of the Silesian Medical University in Katowice, Katowice, Poland
² Clinical Department of Internal Diseases, Allergology and Clinical Immunology, Medical University of Silesia, Katowice, Poland
³ Department of Neurology, School of Health Sciences, Medical University of Silesia in Katowice, Leszek Giec Upper-Silesian Medical Centre of the Silesian Medical University in Katowice, Katowice, Poland

Corresponding author:
Marcelina Niemiec-Urbańczyk, MD, Department of Laryngology and Laryngological Oncology, Leszek Giec Upper-Silesian Medical Centre of the Silesian Medical University in Katowice, Poland ul. Ziołowa 45, 40-635 Katowice, +48 32 359 80 00, marcelina.niemiec@gmail.com

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Key words: inflammation, rhinosinusitis, stroke, thrombectomy.
What’s new

Currently, there are numerous reports emphasizing the relationship between chronic inflammatory diseases and cardio-cerebro-vascular diseases (CCVDs).

In previous reports (retrospective cohort studies) describing the relationship between chronic rhinosinusitis and the occurrence of stroke (ischemic or haemorrhagic), rhinosinusitis was diagnosed based on available codes used in the International Classification of Disease-10 (ICD-10). In our study the presence of sinus inflammatory changes was determined on the basis of computed tomography of the head performed in the ultra-acute period of the disease (up to 6 hours after the first stroke symptoms).

Our study has shown that in ischemic stroke patients who underwent thrombectomy, sinus inflammation was significantly more common than diabetes mellitus and nicotinism, and as common as atrial fibrillation.

The labyrinth of anterior and posterior ethmoid cells covered with mucosa of a relatively large area and the presence of arterial vessels might favour a faster flow of inflammation-promoting mediators.
Abstract

Introduction: Chronic rhinosinusitis (CRS) is one of the most widespread chronic diseases in the world, whereas stroke is a leading cause of death and disability. There are numerous reports emphasizing the relationship between chronic inflammatory diseases and cardio-cerebro-vascular diseases (CCVDs).

Objectives: The aim of the study was to assess whether sinus inflammatory changes can be a risk factor for stroke similar to other known risk factors such as arterial hypertension, atrial fibrillation, arteriosclerosis, diabetes mellitus or smoking.

Patients and methods: The authors of the study analysed the results of sinus computed tomography (CT) performed in 163 ischemic stroke patients (79 men), mean (SD) age 68.5 (12.7) years, qualified for mechanical thrombectomy. The control group consisted of 75 patients (31 men) with neurological diseases of non-vascular origin.

Results: In the group of stroke patients, sinus inflammatory changes were found in 95 subjects (58.3%), with a frequency comparable to the occurrence of atrial fibrillation (77; 47.2%). CRS was statistically more frequent than diabetes mellitus (33; 20.2%, \( P < 0.001 \)), self-reported nicotinism (18; 11.0%, \( P <0.001 \)), less frequent than arterial hypertension and generalized arteriosclerosis (124; 76.1%, \( P < 0.001 \) and 116; 71.2%, \( P = 0.02 \), respectively). Sinus inflammatory changes of moderate or severe intensity were observed more frequently in the group of stroke patients than in the control group and they involved mainly the ethmoid sinuses.

Conclusion: Moderate to severe inflammatory changes indicating chronic rhinosinusitis are common in stroke patients, which suggests the role of local inflammation in inducing acute cerebral ischemia.
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 US population [3, 4]. There are known complications of CRS resulting from the anatomical proximity of the sinuses and the brain, such as brain abscesses, subdural empyema, cranial nerve palsy and meningitis. Chronic rhinosinusitis can lead to cavernous sinus and jugular vein thrombosis, and mycotic aneurysm [5-10]. There is also a relationship between chronic inflammatory diseases and cardio-cerebro-vascular diseases (CCVDs) [11]. Previous cohort studies revealed that patients with CRS were at a higher risk of acute myocardial infarction (AMI) and stroke [12-16].

The aim of the study was to answer the question whether sinus inflammatory changes may be a risk factor for ischemic stroke comparable to arterial hypertension (HA), atrial fibrillation (FA), arteriosclerosis (AO), diabetes mellitus (DM) or smoking. The authors compared the CT scans of paranasal sinuses of patients qualified for mechanical thrombectomy due to ischemic stroke with patients with central nervous system (CNS) diseases of non-vascular origin and analysed the extent of inflammation in individual paranasal sinuses in both groups of patients, aiming to assess in which sinus groups the inflammatory changes were the most advanced.

Patients and methods

This single-centre retrospective observational case-control study included patients referred to the Department of Neurology of the Upper-Silesian Medical Centre in Katowice–Ochojec in 2019. Eligible patients were those with ischemic stroke indicated for mechanical thrombectomy in accordance with 2018 Guidelines for Management of Acute Ischemic Stroke [17]. The patients in whom the results of the performed diagnostic tests confirmed the presence of embolic material in the cerebral vessels were selected.
The control group (CON) consisted of patients with neurological diseases of non-vascular origin (ICD10: G20, G30, G40, C71, G96). Patients with vascular brain injury (≥ 2 Fazekas score) and those treated with thrombolytic or endovascular therapy for at least 3 months prior to study enrolment were not qualified. During hospital stay, the patients underwent several imaging examinations of the head (tomography, angiography of the cerebral vessels using computed tomography, nuclear magnetic resonance NMR) to diagnose the underlying disease. Tomographic examination also made it possible to assess the extent of inflammation within the paranasal sinuses.

In both groups, the authors assessed the extent of the inflammatory process in the paranasal sinuses based on a CT scan, without contrast enhancement, performed on the first day of hospitalization using an Optima CT 540. In the stroke group, CT was performed on the first day of hospitalization, and in the control group within the first three days of hospital stay, to exclude the possibility of hospital-acquired sinus inflammation.

The sinuses were assessed in three planes. The inflammatory lesions were assessed according to 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, the following categories of CRS severity were distinguished: 0 - nonnormal, 1 to 3 - mild, 4 a 10 - moderate, >10 severe. The authors use the term CRS conventionally considering only sinus inflammatory changes visible in the head CT scan, without data on clinical complaints and treatment, as suggested by EPOS [18, 19].

In both groups, the interview data included information on sex, age of patients, comorbidities such as arterial hypertension (HA), diabetes mellitus (DM), arteriosclerosis (AO) (as symptomatic ischemic heart disease during the last 6 months and / or carotid stenosis and / or
lower limb ischemia), atrial fibrillation (FA), smoking cigarettes, C-reactive protein (CRP) values in both groups were also assessed.

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

Statistical analysis

Results are expressed as absolute numbers and percentages for frequencies, mean and standard deviation for age or median values with interquartile ranges for the Lund-Mackay score. The nonparametric Mann-Whitney U rank sum test was used. Comparisons between frequencies were performed with Z-test for proportions. Multiple regression analysis was performed with age, sex, occurrence of atrial fibrillation, arterial hypertension, diabetes mellitus and atherosclerosis to determine the association with values of Lund-MacKay scale in both groups. All analyses were performed with a software package (The STATISTICA 13.3, StatSoft Poland). P values less than 0.05 were considered significant.

Ethics

The Ethics Committee was asked whether the treatment and research required special approval. In response, it was stated that the conducted observation and treatment did not require the consent of the Ethics Committee, because they did not differ from the applied standards of treatment.

Results

The study included 165 patients with ischemic stroke. Two patients in whom a CT scan was performed in a different centre were disqualified. Eventually data from 163 patients (79 men and 84 women) were included into the analysis. 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, mean (SD) age 55.4 (22.4) years.

*Chronic rhinosinusitis in STROKE and CONTROL groups.*

Sinus inflammatory changes were found in 95 (58.3%) patients from the STROKE group, with the following severity: mild - 35 patients; 36%, moderate - 44; 46%, severe -16; 17%.

In the CONTROL group sinus inflammatory changes, were revealed in 34 patients (45.3%). They were mild (L-M <4) in the majority of patients (24; 71%) and moderate in 10 (29%) patients.

The comparison of the stroke group with the control group showed that sinus inflammatory changes were more common in the former group, but non-significantly (95; 58.3% vs. 34; 45.3%, $P = 0.055$). When patients with low L-M values, i.e. between 0-3, were treated as patients without CRS, CRS defined in this way occurred significantly more frequently in the stroke group than in the control group (60; 36.8% vs. 10; 13.3%, $P < 0.001$).

The severity of rhinosinusitis assessed by the LM score was significantly higher in the stroke group (median and IQR: 2; 0-5 vs 0; 0-2, $P = 0.001$), and significantly more patients had the severe sinus inflammatory changes (L-M>10, n = 16; 17% vs n = 0). Tab. 2

*Coexistence of other diseases in the STROKE and CONTROL groups*

In the group of patients who underwent mechanical thrombectomy for ischemic stroke, CRS was found in 95 subjects (58.3%), with a frequency comparable to FA (77; 47.2%). CRS was statistically more frequent than DM (33; 20.2%, $P<0.001$) and the reported history of nicotineism (18; 11.0%, $P < 0.001$), and less frequent than HA and AO (124; 76.1%, $P < 0.001$ and 116; 71.2%, $P =0.02$, respectively). Tab.1

In the control group, CRS was observed in 34 subjects (45.3%), more often than FA (6; 8%, $P < 0.001$), DM (10; 13.3%, $P < 0.001$), AO (15; 20%, $P < 0.001$) and nicotineism (17; 22.6%, $P = 0.005$), and equally often as HA (34; 45.3%, $P = 1.0$). Tab.1
CRP values were comparable in both groups. In the group of stroke patients, atrial fibrillation, arterial hypertension, and generalized arteriosclerosis were significantly more frequent, whereas diabetes mellitus was comparably frequent. The reported history of nicotinism was significantly more frequent in the control group than in the stroke patients. Tab. 1.

Multiple regression including age, sex, occurrence of atrial fibrillation, arterial hypertension, diabetes mellitus and atherosclerosis found that intensity of chronic rhinosinusitis was only associated with male sex in the STROKE group ($P=0.04$) and with no of the examined factors in the CONTROL group. In the STROKE group there were significantly more male patients (58 [73%]) with CRS than without CRS (21 [27%], $P < 0.001$).

Assessment of the extent of inflammatory changes in individual sinuses in the STROKE and CONTROL groups

Another aim of the paper was to assess which sinuses were most often affected by the inflammatory process with the L-M score of more than 3 points. It was found that only the ethmoid sinuses were affected by inflammation of more than 3 points. Inflammatory changes with the L-M score of less than 3 points were equally common in all evaluated sinuses. Tab.3

In the control group, the maxillary and ethmoid sinuses were most often affected, whereas the extent of inflammation over 3 points in the L-M staging system was observed only in the ethmoid sinuses. Tab.3

Discussion

The aim of the study was to check whether chronic inflammation in the paranasal sinuses could be considered a risk factor of 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 sinus inflammatory changes was determined on the basis of computed tomography of the head performed in the ultra-acute period of the disease (up to 6 hours after the first stroke symptoms). Sinus
inflammatory changes detected by CT of the head were objective confirmation of chronic inflammation of varying severity, which could not be related to hospital-acquired infection due to the fact that it was performed on the first day of hospitalization. No changes in the sinuses suggesting cancerous tumours (bone infiltration and destruction, spread beyond the sinuses) were found. Patients hospitalized for reasons other than ischemic stroke, who also underwent sinus CT on the first days of their hospitalization as part of the diagnostic work-up, were selected as the control group.

Our study has shown that in ischemic stroke patients who underwent thrombectomy, sinus inflammation was significantly more common than DM and nicotinism, and as common as FA. FA and nicotinism are recognized and significant risk factors for stroke. Changes suggesting CRS were less common in stroke patients than arterial hypertension and arteriosclerosis. A comparable frequency of CRS was demonstrated in the group of stroke patients and the control group ($P = 0.055$). Sinus inflammatory changes with L-M score $>3$ were significantly more frequently found in stroke patients. Sinus inflammatory changes from 1-3 usually do not have clinical significance. They are often small, unilateral, which is why it seems right to omit this group of patients when comparing the occurrence of CRS in the studied groups.

In the group of stroke patients, inflammation most often involved the surrounding sinuses, the so-called ostiomeatal complex, i.e. ethmoid, frontal and maxillary sinuses. The greatest severity of the inflammatory process (L-M $>3$) was observed in the ethmoid sinuses. The ethmoid sinuses built from multiple minor cells covered by mucosa have relatively big surface in comparison to their capacity. These are the only sinuses with vessels running within (anterior and posterior ethmoid artery) often without bone canal what leads to direct contact with the inflammatory changed mucosa. It may facilitate the flow of the inflammatory mediators in the vessels. The anterior ethmoid cells are contiguous with the nose through an important anatomic region - the ostiomeatal complex. This area is of primary importance in 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]

It is worth emphasizing that CRS was much more common in both groups than in the general population (5-12%) [18]. When examining the incidence of CRS in the Dutch population, de Loos [21] stated that 12.8% subjects had epidemiologically (symptom-) based CRS, and of these subjects 23% had L-M score of 4 or greater. The prevalence of clinically (imaging-) based CRS was 3% or 6.4%, depending on the cut-off point. In subjects with abnormalities at imaging (L-M > 4), only 21% had epidemiologically based CRS.

CRS was diagnosed based on inflammatory changes visible in sinus imaging. The limitation of the study was the lack of data from the history of sinus complaints and possible treatment in accordance with the EPOS 2020 guidelines [19]. There were no results of subjective tests, such as the visual analogue scale (VAS) [22] or the Sino-Nasal Outcome Test -22 (SNOT-22) [23], or accurate data on inhalation allergy, bronchial asthma and hypersensitivity to non-steroidal anti-inflammatory drugs (NSAIDs).

There are reports in the literature claiming that patients with chronic inflammatory diseases have a higher risk of coronary heart disease, peripheral vascular disease, cardiomyopathy and stroke [24,25]. Inflammation also promotes the development of arteriosclerosis. The effects of chronic inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, psoriasis on the cardiovascular system are known [26,27,28]. The inflammatory cytokines involved in CRS such as C-reactive protein (CRP) and interleukin-1 (IL-1) or IL-17 have also been speculated to play a role in the development of stroke [29,30]. IL-1 may result in perivascular inflammation and progress of internal carotid artery thrombosis. IL-17, particularly in combination with TNF-α, promotes pro-inflammatory, pro-coagulant ant pro-thrombotic effects in blood vessels [31]. The effect of proinflammatory cytokines is endotheliopathy
resulting in adverse modulation of cerebral flow and nerve tissue perfusion parameters. At the sites of the diseased vessel wall, there occur clots, aneurysms, wall rupture with local haemorrhage. Platelets can be directly activated by bacterial antigens or via activated leukocytes [32]. Bacterial LPS (a paradigm of acute infection with Gram-negative bacteria) can induce stroke in rats with existing risk factors (old age, arterial hypertension, diabetes mellitus) [33]. It is worth noting that rich bacterial flora is present in the sinuses, and the presence of Gram-negative bacteria is significantly more common in the group of patients over 65 years of age, which was observed in our previous studies [34]. In this group of patients, comorbidities such as arterial hypertension and diabetes mellitus are more common. In our study, larger sinus inflammatory changes were observed in the group of older stroke patients, whereas Lee [15] stated that the risk of stroke in patients with CRS was greater in the group of patients under 60 years of age. Previous reports (retrospective cohort studies) describing the relationship between CRS and the occurrence of stroke (ischemic or haemorrhagic) were carried out in a different methodological way [13, 15, 35]. Rhinosinusitis was diagnosed based on available codes used in the International Classification of Disease-10 (ICD-10). Objective imaging tests or subjective scores of inflammation assessment were not analysed. Nevertheless, the results of such analyses confirmed that CRS is an important risk factor for stroke. Patients diagnosed with CRS chronically use drugs that reduce nasal mucosa congestion, which affects blood pressure and heart rate and can further contribute to the onset of stroke. In addition, frequent use of systemic and locally acting steroids is not insignificant [36]. In epidemiological studies, a strong relationship was found between cigarette smoking and CRS [37,38,39,40]. Cigarette smoking is also an important risk factor for stroke, dependent on the
dose and increasing mortality by around 15% [40,41]. In our studies, nicotinism was less common than sinus inflammatory changes.

Studies on the type of involved sinuses suggest that particular attention should be paid to pathology within the ethmoid sinuses. The labyrinth of anterior and posterior ethmoid cells covered with mucosa of a relatively large area and the presence of arterial vessels might favour a faster flow of inflammation-promoting mediators.

Our results justify particular attention to the paranasal sinuses in patients who have suffered from or are at risk of ischemic stroke.

When moderate or severe CRS is diagnosed in these patients, intensive maximal medical therapy or interventional treatment should be started as early as possible, as this may prevent stroke and associated complications.

In the future, it is worth planning studies assessing the potential impact of CRS on the course of the acute phase of stroke, the effect of therapy and the degree of post-stroke disability.

Moderate and severe chronic inflammatory changes in the sinuses, especially in the ethmoid sinuses, are common in stroke patients, which suggests the role of local inflammation in inducing acute cerebral ischemia.

**Contribution statement:** GSM conceived the idea for the study, GSM and ALB contributed to the design of the research, all authors were involved in data collections, GSM, JG, MNU analyzed the data, GSM, JG, MNU edited the final version of the manuscript, all authors approved the final version of the manuscript.
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Table 1. Clinical characteristics of patients.

|                             | Stroke  | Controls | \(P\) |
|-----------------------------|---------|----------|--------|
|                             | N = 163 | N = 75   |        |
| Mean age (mean SD)          | 68.5 (12.7) | 55.4 (22.4) | <0.001 |
| Sex: m/f n                  | 79/84   | 31/44    | 0.3    |
| Atrial fibrillation n, %    | 77; 47.2% | 6; 8%    | <0.001 |
| Arterial hypertension n, %  | 124; 76.1% | 34; 45.3% | <0.001 |
| Diabetes mellitus n, %      | 33; 20.2% | 10; 13.3% | 0.2    |
| Arteriosclerosis n, %       | 116; 71.2% | 15; 20%  | <0.001 |
| Smoking n, %                | 18; 11% | 17; 22.6% | 0.02   |
| CRP, mg/l (median, IQR, and total range) | 9.5 (5-17.5; 5-163) | 10.3 (5-15.8; 5-91.6) | 0.051 |

CRP – C reactive protein, IQR - interquartile range, SD - standard deviation
Table 2. Occurrence of sinus inflammatory changes in the study groups, broken down by severity levels.

| CRS L-M >1 n, % | Stroke group | Controls | P  |
|-----------------|--------------|----------|----|
| L-M score (median, IQR and total range) | | | |
| Mild (1-3) n, % | 35; 37% | 24; 71% | <0.001 |
| Moderate (4-10) n, % | 44; 46% | 10; 29% | 0.08 |
| Severe (>10) n, % | 16; 17% | 0; | NA |
| CRS L-M >3 n, % | 60; 36.8% | 10; 13.3% | <0.001 |

CRS (chronic rhinosinusitis), IQR (interquartile range), L-M (Lund-Mackay score), NA (not applicable)
Table 3. CT inflammatory changes in various sinuses in STROKE and CONTROL groups.

| Severity of sinus inflammatory changes according to the L-M staging system (points) | Sinus | STROKE N=95 | CONTROLS N=34 | STROKE N=95 | CONTROLS N=34 | STROKE N=95 | CONTROLS N=34 | STROKE N=95 | CONTROLS N=34 |
|---------------------------------|-------|-------------|---------------|-------------|---------------|-------------|---------------|-------------|---------------|
| 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            |
| Number (%) of patients with changes in particular sinuses of any severity |       | 71 (74.7%)  | 15 (44.1%)    | 37 (38.9%)  | 9 (26.5%)     | 44 (46.3%)  | 10 (29.4%)    | 55 (58%)    | 20 (58.8%)    |
| Comparison between the groups   |       | P=0.001     | P=0.19        | P=0.08      | P=0.93        |
| Number of patients with changes in particular sinuses with points 4-6 (% of all patients with changes in a particular sinus) |       | 28 (39.4%)  | 5 (33.3%)     | 0           | 0             | 0           | 0             | 0           | 0             |
| Number of patients with changes in particular sinuses with points 1-3 (% of all patients with changes in a particular sinus) |       | 43 (60.6%)  | 10 (66.6%)    | 37 (100%)   | 9 (100%)      | 44 (100%)   | 10 (100%)     | 55 (100%)   | 20 (100%)     |

* P<0.001 ethmoid vs sphenoid sinuses; P=0.001 ethmoid vs frontal sinuses; P=0.01 ethmoid vs maxillary sinuses in STROKE group
L-M (Lund-Mackay)