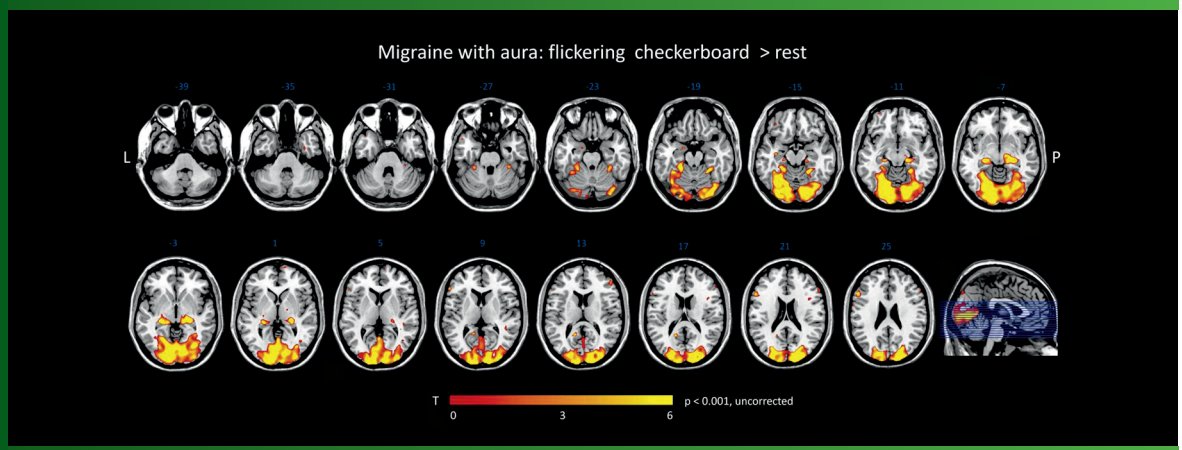
Neurologia i Neurochirurgia Polska, 2019, vol. 53, no. 4

NEUROLOGIA I NEUROCHIRURGIA POLSKA

POLISH JOURNAL OF NEUROLOGY AND NEUROSURGERY

The Official Journal of Polish Neurological Society

2019, vol. 53, no. 4



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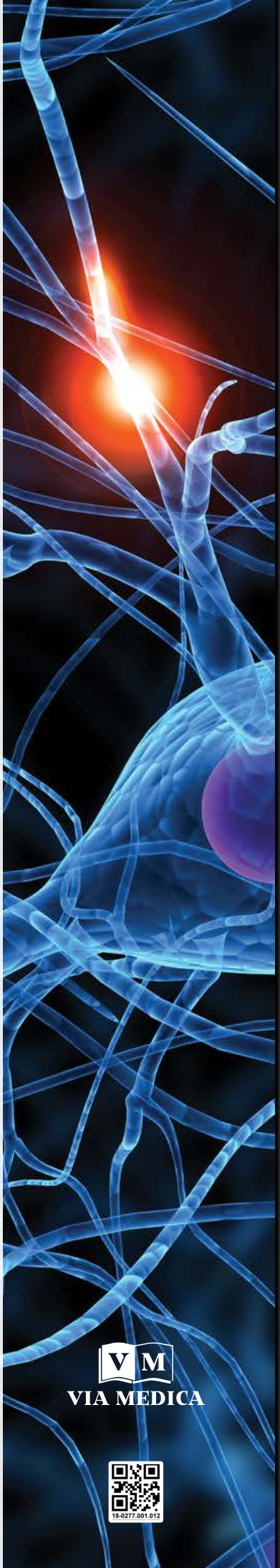

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NEUROLOGIA I NEUROCHIRURGIA POLSKA

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Neurologia i Neurochirurgia Polska also known under the name of *Polish Journal of Neurology and Neurosurgery (PJNNS)* is a premier research and educational platform of the Polish Neurological Society and Polish Society of Neurosurgeons. It has a long and accomplished history dating back to earlier days of the XX Century. The journal publishes the results of basic and clinical research contributing to the understanding, diagnosis, and treatment of neurological and neurosurgical disorders.

Neurologia i Neurochirurgia Polska (ISSN: 0028-3843) is published 6 times a year by VM Media sp. z o.o. VM Group sp.k.

Editorial Address: VM Media sp. z o.o. VM Group sp.k.
ul. Swietokrzyska 73, 80–180 Gdansk,
tel: (+48 58) 320 94 94, fax: (+48 58) 320 94 60
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Current Impact Factor of Neurologia i Neurochirurgia Polska (2018) is 1.006

Editorial policies and author guidelines are published on journal website:
www.journals.viamedica.pl/neurologia_neurochirurgia_polska

Cover photo: Paweł Kreczmański et al., Activations in response to a flickering checkerboard in migraine with aura, see figure on page 302

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POLISH JOURNAL OF
NEUROLOGY
AND NEUROSURGERY

The Official Journal of Polish Neurological Society

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INVITED EDITORIAL

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2019, Volume 53, no. 4, pages: 239–241
DOI: 10.5603/PJNNS.2019.0038

ISSN 0028–3843

Treatment with istradefylline for postural abnormalities in Parkinson's disease

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ABSTRACT

Introduction. In the current edition, Fujioka and colleagues report on four Japanese patients with Parkinson disease (PD) and severe postural abnormalities treated with istradefylline (adenosine A2A receptor antagonist); further, dopamine agonists were withdrawn. Three patients experienced significant improvements of postural abnormalities.

Clinical reflections. Postural abnormalities in PD include camptocormia, antecollis, lateral trunk flexion, and scoliosis. They may be very pronounced and significantly reduce quality of life. The therapy of postural deformities in PD is currently disappointing.

Clinical implications. Effective therapeutic strategies for postural deformities in PD are an unmet need. Larger clinical trials investigating novel approaches including istradefylline are warranted.

(*Neurol Neurochir Pol 2019; 53 (4): 239–241*)

Istradefylline is a selective adenosine A2A receptor (A2AR) antagonist, which is approved for treatment in patients with Parkinson's disease (PD) in Japan. It has been submitted for FDA approval for use as adjunctive treatment to L-dopa in patients with PD experiencing OFF episodes. Fujioka and colleagues describe four Japanese patients with PD and postural abnormalities (antecollis, "Pisa syndrome", and camptocormia), in whom treatment with istradefylline was initiated [1]. Further, their dopaminergic medication was discontinued simultaneously or up to two months before starting istradefylline. Three patients had well-preserved paraspinal muscle volume and showed moderate to very good improvement of postural abnormalities. The fourth patient had moderate paraspinal muscle atrophy and experienced no improvement of her antecollis. In conclusion, istradefylline may be a novel therapeutic strategy for postural abnormalities in PD.

Postural abnormalities in Parkinson's disease include camptocormia, antecollis, lateral trunk flexion (LTF, "Pisa syndrome") and scoliosis. The term "camptocormia" was coined in 1915 [2]. The syndrome was initially described by Brodie in 1937 as "hysterical bent back" [3]. Since consensus criteria for camptocormia are lacking, thoracolumbar flexion angles of ≥ 45 degree are generally chosen for the diagnosis. Accordingly, the estimated prevalence of camptocormia varies (3–18%). Camptocormia and LTF are generally aggravated by walking or exercising and alleviated by lying supine, standing against a wall, using walking support, or in few instances by wearing a low-slung backpack, thus exhibiting features of dystonia, including a "sensory trick" [4, 5]. Scoliosis, however, remains fixed, and its diagnosis requires imaging of the spine [5]. Postural deformities are more frequent in female patients with PD, who are older, have more advanced disease, and they appear to occur more frequently in Asia. A recent study reported that 9/18 patients with PD and postural deformities (≥ 1 point on the UPDRS III item "posture"; all patients were examined in the ON state) showed improved posture during istradefylline treatment. The patients who responded had higher Hoehn and Yahr stages [6]. A positive response to istradefylline was further observed in a case series, in which camptocormia was mostly OFF-state associated [7].

The etiology of postural abnormalities in PD remains poorly understood [4, 5, 8]. Camptocormia in PD was reported to

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worsen in the OFF state and thus suggested to arise due to rigidity. Further etiologies of camptocormia include primary and secondary myopathy, proprioceptive dysregulation, dystonia, inflammation/myositis as well as functional and medication-induced disorders. Additionally, an impaired perception of verticality is associated with postural abnormalities in PD [4, 5, 8]. Medications that may cause postural abnormalities include dopamine agonists, anticholinergics, and amantadine. The notion that dopamine agonist may induce reversible postural abnormalities is currently based on case reports, which mostly stem from Japan [9–15]. L-dopa and dopaminergic agents may worsen, improve or not alter postural abnormalities in PD [4, 16]. Finally, a consistent myopathic lesion pattern was seen in paraspinal muscle biopsies of patients with camptocormia and PD [17].

Transgenic mice with the DYT1 mutation showed reduced dopamine D2 receptor (D2R) protein and reduced ability of D2Rs to activate their cognate Go/i proteins. Resulting synaptic plasticity impairment was fully restored by pharmacological blockade of A2ARs [18]. Thus, istradefylline may improve dystonic components of postural abnormalities. Further, istradefylline may reduce rigidity by inhibiting basal ganglia output through an indirect pathway; it may reduce the cholinergic output of the pedunculopontine nucleus (PPN) [19–20]. The PPN is assumed to reduce muscle tone via α- and γ-motoneurons. Blockage of GABAergic nucleus accumbens output to brainstem centers including the mesencephalic locomotor region has also been postulated [21].

Current treatment of postural abnormalities in PD is challenging. Regarding injections with botulinum toxin *i.m.*, differentiation between upper and lower camptocormia has been proposed [4], since different muscles appear involved in these two distinct types of camptocormia. In most studies, the rectus abdominis and the iliopsoas muscles were injected [4]. Some success was achieved using 1% lidocaine [22]. Other pharmacological options include trihexiphenidyl, baclofen, amantadine, biperiden, tetrabenazine, clonazepam and bromazepam; efficacy, however, is considered disappointing [4, 5 ,8]. L-dopa improved posture in about 20% of patients with PD [16]. One case series found that *i.v.* L-dopa infusions improved camptocormia and antecollis in PD, especially when abnormal postures were OFF-state associated [23]. Surgical approaches include deep brain stimulation (of about 80 patients, about 60% showed improvement of posture); orthopedic spinal correction, and unilateral pallidotomy [8]. Lastly, physiotherapy can achieve improvements.

Several randomized placebo-controlled studies including multicenter phase 3 studies (https://clinicaltrials.gov/), meta-analyses, and reviews [24–27] evaluating the efficacy of istradefylline in PD are available. Overall, istradefylline is considered to decrease OFF time duration and improve motor features in PD. However, not all studies reported positive results [28]. Several studies found only moderate improvements. E.g., the KW-6002-US-2018 study showed only modest changes in UPDRS III scores, and istradefylline did not significantly impact OFF time duration [29]. One meta-analysis found positive results only for istradefylline 40 mg/d but not 20 mg/d [25]. In a recent post-marketing surveillance study, UPDRS III scores decreased from 33.7 to 29.2 after treatment over one year; OFF time duration was reduced in only 38.2% of the patients [30]. While adverse effects like dyskinesia or nausea do occur, istradefylline is generally considered well tolerated.

In summary, postural abnormalities in PD can be very severe, and therapeutic strategies are an unmet need. Thus, larger clinical studies on therapeutic approaches are warranted, both regarding surgical procedures and pharmacological approaches including novel agents like A2AR antagonists.

Conflict of interest: *none*

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INVITED REVIEW ARTICLE

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2019, Volume 53, no. 4, pages: 242–250
DOI: 10.5603/PJNNS.a2019.0032

ISSN 0028–3843

Acute bacterial meningitis and stroke

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ABSTRACT

Introduction. Acute bacterial meningitis remains a common disease, especially in developing countries. Although advances over the last century have improved mortality and morbidity, the neurological adverse effects remain high. Specifically, acute ischaemic stroke is a serious comorbidity that represents both disease severity and poor prognosis. This review presents the clinical connection between meningitis and stroke, and discusses the neuroinflammatory components that have direct ties between these diseases.

State of the art. Ischaemic stroke is the direct result of the inflammatory response produced to eradicate infectious pathogens. Bacterial virulence factors and pathogen-associated molecular patterns cause direct damage to the blood-brain barrier and trigger leukocytes to react to the infection. Cytokines are released that cause further destruction of the blood-brain barrier, lead to neuronal death, and recruit the prothrombotic effects of the coagulation cascade through the complement system. Unfortunately, this inflammatory response causes vasculopathy and hypercoagulation of the cerebral blood vessels, leading to cerebral ischaemia.

Clinical implications. Pharmacological attempts to mitigate this inflammatory response have produced both positive and negative results. On the one hand, corticosteroids have been shown to improve mortality if given early in patients with bacterial meningitis, particularly pneumococcal meningitis. On the other hand, corticosteroids have been linked to delayed cerebral infarction and other adverse effects.

Future directions. New targets for specific inflammatory markers have shown success in rodent models, but have not yet been proven beneficial in humans. Genetic markers are on the horizon, and may serve as individualised targets for diagnosis and therapy.

Key words: bacterial meningitis, neuroinflammation, pneumococcal meningitis, stroke

(*Neurol Neurochir Pol 2019; 53 (4): 242–250*)

Introduction

Acute bacterial meningitis (ABM) has an incidence in developed countries of between 0.7 and 0.9 per 100,000, but its incidence remains as high as 40 per 100,000 in developing countries [1]. Risk factors for ABM are those which cause an immunocompromised state, and include age (infants and > 65 years), splenectomy or hyposplenia, HIV/AIDS, cancer, organ transplant, and nutritional states such as diabetes mellitus and alcoholism [2]. Environmental factors, specifically warmer climates, also increase the risk of some causes of ABM [3]. Before the introduction of antibiotics in the 1930s, ABM was nearly universally fatal [4]. In subsequent decades, pathogen-specific antimicrobials, vaccinations toward encapsulated pathogens, and the addition of corticosteroids into treatment management have all contributed to improving rates of mortality and morbidity [1]. Prior to incorporating corticosteroids into acute treatment regimens, mortality was from 19% to 24%, and serious morbidity 34% to 52% [5–7]. Even with contemporary treatment plans, mortality remains as high as 20% in some reports [8–10]. One particular adverse effect of ABM is cerebral ischaemia (CI), which is both an indicator of ABM disease severity, and an independent predictor of a poor clinical outcome.

In this review, we will discuss the association and causes of CI in ABM, describe the clinical consequences of the

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inflammatory response to ABM, and analyse how current treatment modalities, particularly corticosteroids, may have both positive and negative consequences on ABM. We will limit ABM to encapsulated pathogens (*Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenza*) because these are the most common causes of meningitis, and the best-studied in regards to CI.

CI and ABM

Before contemporary treatment regimens, between 50% and 75% of patients with ABM had a neurological or systemic adverse event [5, 6]. Among the most common acute neurological adverse effects were cerebrovascular disease (10–29%), cerebral oedema (14–29%), hydrocephalus (12–16%), and intracerebral haemorrhage (1–9%) [5, 6, 11, 12].

Patients with ABM-associated CI have high mortality (46%) and morbidity (38–62%) [12, 13]. Risk factors for CI include otitis or sinusitis, and being immunocompromised [12, 14]. Patients who present with a lower Glasgow Coma Scale (GCS) score, lower levels of cerebrospinal fluid (CSF) leukocytes, and higher serum erythrocyte sedimentation rates, also have a higher risk of CI [12, 14]. There are conflicting reports regarding the risk of age and developing CI [12, 14]. Treatment with dexamethasone has been reported as not being a risk factor [14].

Early angiographic studies revealed several potential pathologies for CI, including arterial narrowing, vessel wall irregularities, focal dilatations, arterial occlusions, and thrombosis of the venous sinuses and cortical veins [13]. Interestingly, whether these findings correlate directly with any clinical neurological symptoms has not been reported, and it is not known if these findings could represent acute or chronic vasculopathy, or if any patients had infective endocarditis (IE).

Increased cerebral blood flow velocity, another marker of cerebral vasculopathy and arterial narrowing, is related to ABM-associated CI and poor outcomes [15]. In a retrospective study, an increase in transcranial Doppler cerebral blood flow velocity of greater than 150 cm/s correlated with a poor clinical grade on presentation, an increased risk of CI [odds ratio (OR), 9.15; $P < 0.001$], and an unfavourable outcome (Glasgow Outcome Score, < 4; OR, 2.93; $P = 0.018$). Timing of the transcranial Doppler in the disease course was not standardised, and there were limitations to the conclusions. Of the 41 patients studied, 20 underwent either computed tomography angiography, magnetic resonance angiography, or digital subtraction angiography to characterise the vasculopathy, but only nine had evidence of vascular narrowing revealed by these methods [15].

Vasospasm and vasculitis are not the sole causes of CI. ABM, especially severe ABM, affects the coagulation cascade, causing intravascular thrombus formation [16]. Cerebral thrombosis commonly occurs in pneumococcal meningitis (PM), even without CI or vasculitis. In a case series of 16 patients who died of ABM, nine had CI, but five of these did not have pathological evidence of vasculitis, and none had evidence of large vessel vasculitis [11]. Of the four patients with vasculitis, all had intra-arterial thrombosis [11].

ABM can cause CI by other, less common, mechanisms. Though a rare occurrence in meningitis (~ 2% [17]), IE is a potential source of cerebral infarction. Conversely, ABM occurs in 1-20% of patients with IE [18]. In the co-occurrence of IE and ABM, the ischaemic stroke rate has been reported to be 38%, higher than in either IE or ABM alone [17]. Swift treatment is vital because the risk of stroke decreases by 65% after one week of antibiotic therapy [19]. In addition, either ABM or IE can be the primary source of infection. It has been reported that acute IE (usually caused by *Staphylococcus aureus)* compared to subacute IE (usually caused by viridans streptococci) is more associated with strokes and CSF profiles with neutrophilic pleocytosis, decreased glucose, and positive culture (bacterial meningitis) [20]. Alternatively, ABM, especially PM, can spread systemically, causing acute IE.

Regardless of the primary source, if either ABM or IE is suspected, a thorough clinical examination is necessary, including trending fever curves, and looking for cardiac murmur, Janeway lesions, Roth spots, Osler nodes, nuchal rigidity, and Kernig and Brudzinski signs. All patients with ABM should have blood cultures and a transthoracic echocardiogram to screen for IE.

Finally, CI can be caused by systemic inflammatory responses to ABM, including septic shock (11.6%), acute respiratory distress syndrome (3.5%), and disseminated intravascular coagulation (8.1%) [5]. Studies in rabbits have shown that, like many acute brain injuries, cerebrovascular autoregulation is lost during sepsis [21]. Patients, therefore, can develop watershed strokes during this period of poor cerebral autoregulation and hypoperfusion.

For the purposes of this review, we will focus on the two primary mechanisms by which ABM causes CI: firstly inflammatory vasculopathy (including vasculitis and vasospasm), and secondly intravascular thrombus formation. Radiographic and pathological studies have differed in the predominance of these mechanisms and how these vascular changes cause clinical changes.

Delayed CI

In between 1% and 4% of cases of ABM, patients will have good clinical recoveries initially, but after the first week will develop acute changes in their level of consciousness or develop new focal neurological signs [17, 22, 23]. These abrupt changes are commonly due to delayed CI (DCI). One report described a series of six patients with posterior circulation predominant DCI which occurred more than a week after the initial presentation [22]. After initial treatment, the CSF of these patients became less inflammatory, but developed increased white blood cell count and protein at the time of deterioration. Repeat CSF analyses had negative cultures

and gram stains, suggesting a noninfectious aetiology to the relapsing meningitis. Prognosis was poor as four of these six patients died and two remained disabled. Autopsies on two of these patients showed normal macroscopic vessels without evidence of vasculitis, but with focal thrombi in perforating arteries [22].

In another postmortem study of patients who died from ABM, there was extensive inflammation in the meninges and blood vessels with thrombosis, infarction, and deposition of immunoglobulins M and G in the meninges [24]. There were no differences in these findings between DCI and non-DCI deaths. They also found pneumococci capsules in the meninges as much as 35 days after onset, suggesting that the stimulus for inflammation can remain in the meninges even weeks after treatment [24].

Another study reported that nearly 60% of ABM-related cerebrovascular events occurred more than six days after onset [25], with all patients having an initial improvement of CSF parameters. Pathological studies were not completed, but in these patients there was radiographic evidence of vasculopathy. The most common ischaemic mechanisms were vasospasm and vasculitis, with a larger proportion in the frontal lobe and middle cerebral artery [25].

As with CI, the causes of ABM-associated DCI vary. Inflammatory vasculopathy, including vasospasm and vasculitis, has been seen angiographically, but not always pathologically. Conversely, pathology can reveal thrombosis and signs of hypercoagulation in vessels not identified on angiography. Most likely, both vasculopathy and hypercoagulation are important causes of CI and DCI.

Thus the question is: Why does ABM cause inflammatory vasculopathy and hypercoagulation leading to CI and DCI? The answer lies in the inflammatory cascade initiated by ABM.

Inflammatory response to bacterial invasion of the meninges

What follows the inoculation of an infectious microbial into the subarachnoid space is a reactive inflammatory response designed to destroy and eliminate the infectious pathogen. Bacteria use a variety of virulence factors to invade the subarachnoid space. Initially, bacteremia induces an inflammatory response of the cerebrovascular epithelial cells. Highly vascular areas, such as the leptomeninges, or areas with blood-CSF barriers such as the choroid plexus, are the most likely points of entry from haematogenous spread [26–28]. After bacterial invasion, leukocytes (predominantly neutrophils) quickly migrate into the subarachnoid space. Both bacteria and neutrophils undergo reactions that rapidly increase the inflammatory response, resulting in vasodilatation, breakdown of the blood-brain and blood-CSF barriers, and further migration and activation of inflammatory cells (Fig. 1).

Based on the specific stimulating factor, leukocytes will produce a variety of noncellular inflammatory molecules,

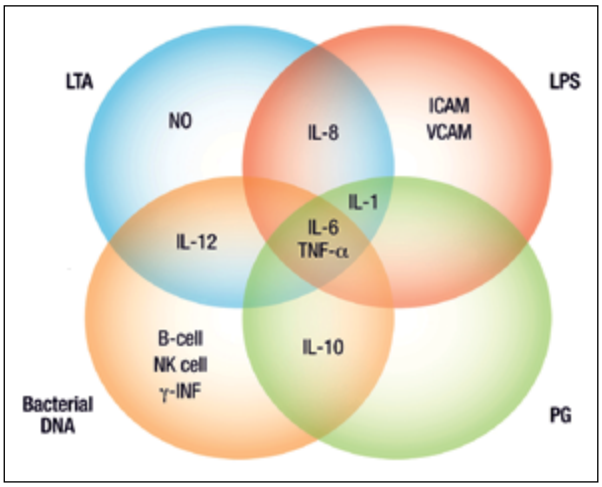

Figure 1. Basic mechanisms of bacterial chemotaxis, drivers of inflammation, and vascular consequences. A, Virulence factors and adhesive proteins, such as CbpA and PilC1, interact with endothelial cells to promote bacterial adhesion and endocytosis. Endothelial cells react by expressing ICAM-1 which binds to LFA-1 (integrin) on leukocytes to promote migration. These leukocytes also produce TNF-α and No synthetase. Leukocytes are then able to permeate into the CSF relatively soon after infiltration of the bacteria and result in No and MMPs, further damaging the BBB and BCB. Pneumolysin, haemolysin/cytolysin, and H_2O_2 are bacterial toxins that stimulate apoptosis, inducing factor caspases, ultimately causing mitochondrial and neuronal death. Bacteria also produce PAMPs of PG, LP, and LPS, which induce indirect neurotoxicity by activation of PRRs on microglia, and promote TLR2 and TLR4 on leukocytes, resulting in neural death. B, The ultimate cerebrovascular consequences of these reactions are: contraction of perivascular smooth muscle, causing vasospasm and vasculitis; activation of the coagulation cascade, causing intravascular thrombi; and breakdown of the vascular basement membrane, causing diffusion of protein and water resulting in cerebral oedema
BBB — blood-brain barrier; BCB — blood-cerebrospinal fluid barrier; Cbp — curved DNA-binding protein; CSF — cerebrospinal fluid; ICAM — intercellular adhesion molecule; LFA — lymphocyte function-associated antigen; LP — lipoprotein; LPS — lipopolysaccharide; LTA — lipoteichoic acid; MMP — matrix metalloproteinases; No — nitric oxide; PAF — platelet-activating factor; PAMPs — pathogen-associated molecular patterns; PG — peptidoglycan; PilC — pilin biogenesis protein; PRRs — pattern recognition receptors; TLR — toll-like receptor. Used with permission of Mayo Foundation for Medical Education and Research. All rights reserved

such as cytokines and chemokines [29] (Fig. 2). Of these, the most commonly expressed include interleukin (IL)-6 and tumour necrosis factor (TNF)-α, followed by IL-1, IL-8, and IL-10 (Tab. 1). Importantly, the liver synthesises the components of the complement cascade, which connect the inflammatory process to the coagulation cascade. The end products of the complement cascade are C5a, C3a, and C5b (which combines with C9 to create the C5a–C9 membrane-attack complex). C5a stimulates tissue factor, which is the pivotal initiator of

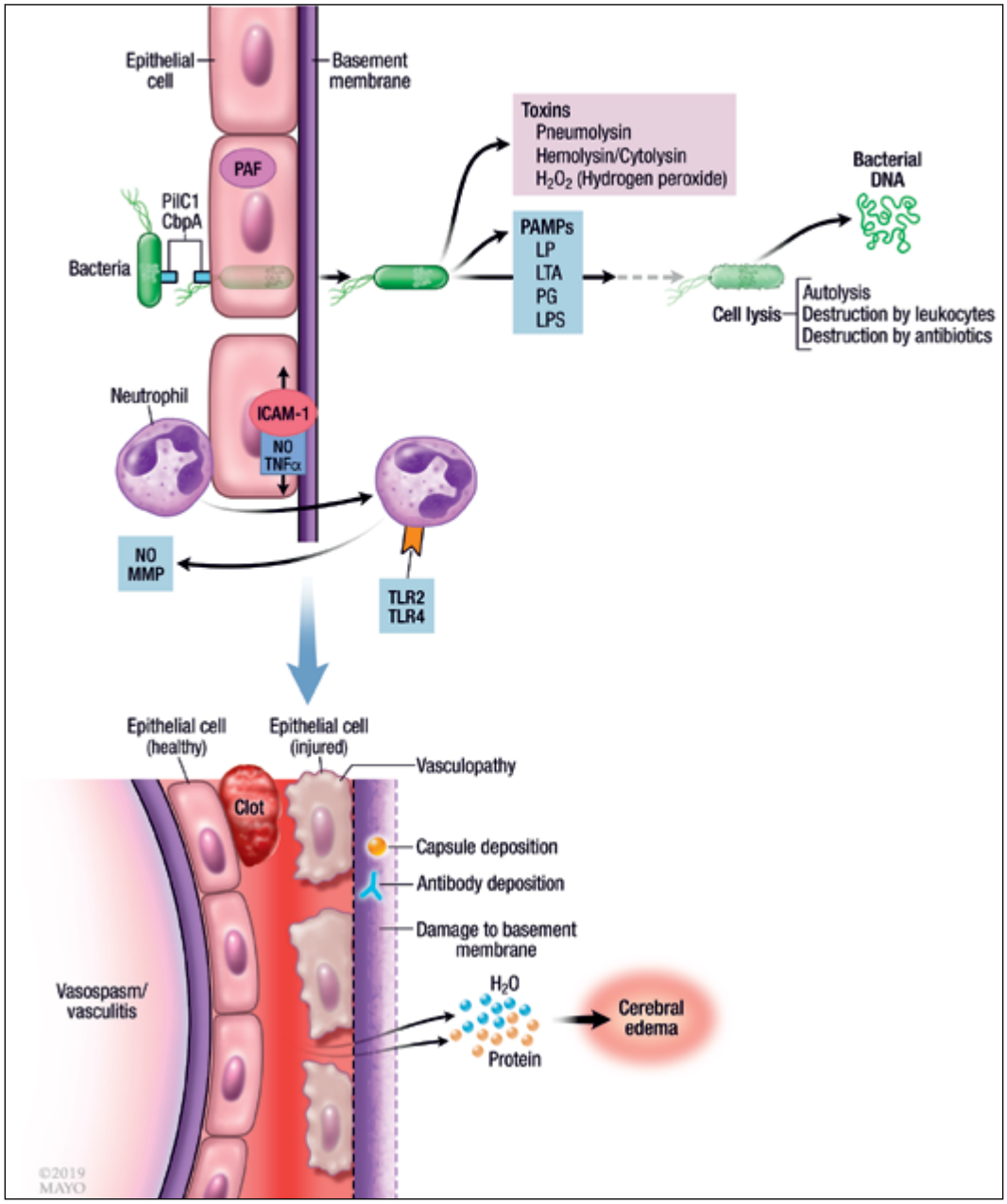

Figure 2. Cytokines and pathogen-associated molecular patterns (PAMPs). Four common PAMPs (LTA, LPS, PG, and bacterial DNA) stimulate the production of various cytokines, with overlap between the PAMPs. IL-6 and TNF-α are stimulated by all four PAMPs
ICAM — intercellular adhesion molecule; IL — interleukin; INF — interferon; LPS — lipopolysaccharide; LTA — lipoteichoic acid; NK — natural killer; NO — nitric oxide; PG — peptidoglycan; VCAM — vascular cell adhesion molecule.

inflammation-induced thrombin generation [30] and stimulates factor Xa of the coagulation cascade. Factor Xa continues to cleave prothrombin into thrombin, which then converts fibrinogen to soluble fibrin. Another role of C5a is to stimulate plasminogen activator inhibitor-1, with the end result of decreased plasmin, and thus decreased thrombolysis. In turn, the coagulation cascade affects the complement cascade in that factor XIIa stimulates the classical complement pathway and thrombin stimulates C5 convertase [31]. The downstream results of this inflammatory response include cerebral oedema, coagulopathy, and direct damage to the neurons, vasculature, basement membranes of the blood-brain and blood-CSF barriers, and ependymal layer of the ventricles [32].

Clinical effects of inflammatory cytokines

Cytokines serve as potential biomarkers for associating the inflammatory response during meningitis with diagnosis,

Table 1. Roles of cytokines

Cytokine	Source	Function
IL-1, TNF	Macrophages, monocytes, dendritic cells, endothelial cells	— Initiate PGE2 in anterior hypothalamus → fever
		— Alter endothelial cell adhesion molecules
		— Increase liver synthesis of:
		• Ferritin
		• Fibrinogen
		• C-reactive protein
		— Increase release of neutrophils from bone marrow and transendothelial neutrophil passage [27]
		— IL-1 may be more potent in BBB destruction [28]
		— TNF promotes apoptosis
IL-6		— Increase liver synthesis of acute phase reactants
IL-8		— Chemotaxis
C3a, C5a (anaphylatoxins)	Liver	— Mast cell release of histamine
		— C5a → activation of neutrophil adhesion molecules
C3b		— Opsonisation (antibody-mediated phagocytosis)
C5a-C9 (MAC)		— Cell lysis
Histamine	Mast cells, platelets, enterochromaffin cells	— Vasodilation
		— Increased venular permeability
Nitric oxide	Macrophages, endothelial cells; free radical gas released during conversion of arginine to citrulline by nitric oxide synthase	— Vasodilation
		— Bactericidal
Serotonin	Platelets	— Vasodilation
		— Increased venular permeability
		— Increased collagen synthesis

BBB — blood-brain barrier; IL — interleukin; MAC — membrane-attack complex; PGE2 — prostaglandin E2; TNF — tumour necrosis factor

disease severity, adverse effects (including stroke), prognosis, and treatment.

ABM is traditionally diagnosed by CSF analysis, specifically by measuring cell counts, leukocyte differential, protein, and glucose, and is ultimately confirmed using gram stain and bacterial culture. However, sometimes these metrics can be inconsistent or inconclusive, especially if antibiotics were administered hours before CSF collection. Inflammatory biomarkers have been shown to be associated with both a positive diagnosis and differentiation of ABM.

In infants younger than six months, IL-6 and IL-10 have been shown to have a strong association with the diagnosis of ABM, even after antibiotics have been administered (area under the receiver operating characteristic curve 0.91 and 0.91, respectively). TNF-α had an area under the curve of 0.88 [33].

In an example of ABM differentiation, CSF levels of IL-1β, IL-2, IL-6, TNF-α, interferon-γ, IL-10, IL-1Ra, IL-8 (CXC chemokine ligand 8), CC chemokine ligand 2 (monocyte chemoattractant protein 1), CC chemokine ligand 3 (macrophage inflammatory protein 1α), CC chemokine ligand 4 (macrophage inflammatory protein 1γ), and granulocyte-colony stimulating factor were investigated in patients with either PM or meningococcal meningitis. Interferon-γ was significantly higher in PM compared to meningococcal meningitis. When the study of CSF was limited to the 48 hours following symptom onset, TNF-α was higher in meningococcal meningitis than PM [34].

CSF cytokines are also correlated with disease severity and prognosis. In 1995, CSF from patients with meningitis was tested for IL-1β, TNF-α, and IL-6. The presence of these CSF cytokines correlated with higher levels of CSF protein and lower CSF glucose, as well as prolonged fever, "fits and spasticity", and death [35]. Although unable to fully illuminate the mechanisms and so delineate why only some patients had these cytokines, these early studies began to build a connection between meningitis and specific inflammatory markers in the cascade.

These results were more recently supported when it was found that in patients with non-meningitis related sepsis, not only were cytokine levels higher in the CSF than in plasma, but also levels of CSF IL-6, IL-8, IL-10, IL-1β, and TNF-α, and plasma IL-10 and IL-12p70 were significantly higher in patients with severe sepsis than in those with sepsis [36].

Additionally, higher CSF levels of IL-6 and IL-12p70 were correlated with worse long-term outcomes [36].

The complement cascade is also associated with disease severity. In normal mice with induced PM, C5a and terminal complement complex (TCC) levels increase from 24 to 48 hours. However, mice deficient of C5a receptor (*C5ar1-/-*) had a less robust inflammatory response and better clinical outcomes. When anti-C5-Abs were administered intrathecally, mice had lower meningitis-related adverse effects and better clinical status compared to systemic administration. In fact, there was no mortality in these mice, and the anti-C5 antibodies outperformed dexamethasone administration [37].

Likewise, higher CSF levels of C5a and TCC in human patients with PM correlated with poor GCS on presentation, high CSF protein and white blood cell count, death, and overall unfavourable outcomes [37]. Median CSF levels of C5a and C5b-9 were higher in patients with ABM-associated DCI than in patients without DCI, although complement levels in patients without DCI were heavily skewed, with several levels higher than observed DCI levels [17]. Therefore, a threshold cannot be established for prediction of DCI.

The increased complement activation also affects the coagulation cascade. Compared to normal patients or those with viral encephalitis, CSF in patients with ABM has higher levels of soluble tissue factor, prothrombin, and plasminogen activator inhibitor-1 [16]. The net effect of these markers is enhanced coagulation and attenuation of fibrinolysis [11].

Clinical implications

The inflammatory response associated with ABM prompted investigation into the use of anti-inflammatory medications to prevent comorbidity. In a landmark trial, dexamethasone was given to patients in conjunction with their initial antibiotics, and when compared to a placebo, showed a lower risk of unfavourable outcome [15% *vs.* 25%; P = 0.03; number needed to treat (NNT), 10], death (7% *vs.* 15%; P = 0.04; NNT, 12.5), impairment of consciousness (11% *vs.* 25%; P = 0.002), seizures (5% *vs.* 12%; P = 0.04), and cardiorespiratory failure (10% *vs.* 20%; P = 0.02) [38]. However, these results were heavily skewed by *Streptococcus pneumoniae*, which was the only pathogen that showed a decreased risk of an unfavourable outcome (26% *vs.* 52%; P = 0.006; NNT, 3.8) or death (14% *vs.* 34%; P = 0.02; NNT, 5) with dexamethasone when compared to a placebo. Patients with PM who received dexamethasone still did poorly compared to the other individual pathogens, highlighting the severe nature of this disease, but suggesting that a large part of its danger is a potentially treatable inflammatory response [38].

Importantly, stroke was not an outcome measure, and its incidence between treatment and control arms was not reported. Because of this study, corticosteroids became part of the standard of care in undifferentiated ABM, though again the effects were perhaps only helpful on PM [39].

After the routine use of dexamethasone in ABM, conflicting reviews and meta-analyses were reported on its usefulness [8–10, 15, 17, 22, 25, 40]. After the implementation of dexamethasone as the standard treatment in ABM throughout the Dutch healthcare system, they observed a 15% decrease in neurological adverse effects, a 10% decrease in deaths, an 11% increase in rate of no or minor disability, an 11% decrease in cranial nerve palsy, and a 10% decrease in hearing impairments [10]. A single centre study found that after initiation of corticosteroids, mortality fell from 24.1% to 5.5% [8]. In a 2015 Cochrane review, corticosteroids were found to reduce hearing loss in children with *Haemophilus influenzae* and mortality in those with PM [9].

However, a meta-analysis of five trials and more than 2,000 patients showed that dexamethasone administration was not associated with a decreased risk of death, disability, or poor functional outcome in all patients, or in any specified subgroup [40]. In fact, the results did not even support the use of dexamethasone in PM [40].

Some studies have suggested that not only might adjunct corticosteroids have a limited role in improving outcome or preventing adverse effects or stroke, but that they might even cause harm. In one case series, corticosteroid use was found in most patients who developed DCI; although most patients who received corticosteroids did not experience DCI, and DCI developed in some patients who did not receive steroids [17]. Furthermore, the study did not report ORs or relative risks of corticosteroids and DCI [17]. Another study reported that all five patients with DCI received corticosteroids, whereas 43 of 115 patients who did not experience DCI received corticosteroids (OR, 13.29) [25]. In this study, the use of corticosteroids appeared to increase the risk of DCI, but it should be pointed out that most patients (90%) who received corticosteroids did not experience DCI. All patients had an initial improvement of CSF parameters, but were severely affected clinically. Only 30% of all ABM patients even received corticosteroids, far less than typically seen as the standard of care [25]. Another series of six patients reported posterior circulation-predominant DCI occurring more than a week after the initial presentation [22]. All patients received corticosteroids and had a good initial recovery before acute deterioration [22]. It has also been reported that patients who received corticosteroids were more likely to have an increase in cerebral blood flow velocity by transcranial Doppler than those who did not (OR, 2.86; P = 0.026), suggesting corticosteroids to be a potential cause of vasculopathy [15]. The authors recognised that in this retrospective study (which included patients prior to the corticosteroid era), many patients probably received corticosteroids because they were not recovering with antibiotics, and so they could not determine whether the severe disease or the corticosteroids directly caused cerebrovasoconstriction [15].

The mechanism of corticosteroid-induced DCI has not yet been fully explained, and reports that describe this association have not been validated by large prospective trials.

Nonetheless, there is a strong relationship between the inflammatory response to ABM and outcomes.

Future directions

Despite the inconsistent results of corticosteroids in reducing comorbidity and stroke, there is still a clear link between the neuroinflammatory response during ABM and the risk of CI. Beyond corticosteroids, our knowledge of cytokines and complement markers has not been incorporated into standard treatment plans. Future work will examine novel anti-inflammatory drugs and genetic targets.

Targeting specific components of the inflammatory cascade has shown promise in animal models. In rats with PM, C1-inhibition reduced clinical illness, produced a less pronounced inflammatory infiltrate around the meninges, produced lower levels of proinflammatory cytokines, and increased bacterial clearance [41]. Intrathecal recombinant TNF-related apoptosis-inducing ligand decreased inflammation and neuronal apoptosis [42]. In an attempt to reduce the inflammatory response of bacteriolysis, the nonbacteriolytic antibiotic, daptomycin, was shown to clear the bacteria faster, reduce matrix metalloproteinase-9 levels, and prevent the development of cortical injury when compared to ceftriaxone [43]. However it must be stressed that these experiments were conducted in rodents, without suitable human trials.

There is hope, however, in trialling specific immunotherapies to reduce central nervous system inflammation from ABM, in much the same way the IL-6 receptor inhibitor, tocilizumab, has been shown to reduce seizure burden in new onset refractory status epilepticus [44].

There are also strong associations between genetics and mortality and disease severity. Polymorphisms in *SERPINE1* and IL-1β are associated with mortality [45]. The single nucleotide polymorphism, rs17611, plays a role in C5 production (GG genotype) and is associated with an unfavourable outcome (OR, 2.25; P = 0.002) [37]. In multivariate regression analysis, including age, CSF white blood cell count, GCS score, blood thrombocyte count, immunocompromised state, otitis media, and sinusitis, rs17611 remained a strong predictor of an unfavourable outcome (OR, 1.91; P = 0.032). It is worth noting that there was no significant association between CSF C5a or TCC levels and rs17611 genotype [37].

Conclusion

ABM remains a serious disease with high rates of morbidity and mortality. Although great strides over the past century have dramatically improved its survivability and the functional outcomes of patients, current therapies do not appropriately target the components of the inflammatory response that occur with this disease. Acute CI, as a common and devastating comorbidity to ABM, is a direct result of this inflammatory reaction, by inflammatory vasculopathy and hypercoagulability. Targeted drugs to reduce the inflammatory response to ABM may also decrease the incidence of CI. This, in turn, will improve survivability and functional outcomes.

Conflict of interest *None.*

Funding *This publication was prepared without any external sources of funding.*

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REVIEW ARTICLE

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2019, Volume 53, no. 4, pages: 251–257
DOI: 10.5603/PJNNS.a2019.0026

ISSN 0028–3843

Electrodiagnostics: MUNE and MUNIX as methods of estimating the number of motor units – biomarkers in lower motor neurone disease

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ABSTRACT

Routine quantitative electromyography is used for the assessment of the presence of lower motor neurone involvement and its consequences, including primary denervation and compensatory reinnervation of muscle fibres. However, it is not useful for the assessment of the motor unit number reserve. The need for a valid biomarker to evaluate lower motor neurone disease progression in such diseases as amyotrophic lateral sclerosis, and for use in clinical trials, has led to a number of studies of the methods that allow assessment of the number of motor units. In this review, motor unit number estimation (MUNE) methods with incremental stimulation and the recently developed motor unit number index (MUNIX) method, along with their technical and clinical aspects, are presented as methods which reflect motor unit loss in neurogenic processes. These electrodiagnostic tests may allow a valuable assessment of disease progression and the efficacy of new therapeutic methods in clinical trials in diseases with lower motor neurone degeneration.

Key words: motor unit, motor unit number estimation, MUNE, motor unit number index, MUNIX, amyotrophic lateral sclerosis

(*Neurol Neurochir Pol 2019; 53 (4): 251–257*)

Introduction

Routine quantitative needle electromyography (EMG) is used for the assessment of the presence of lower motor neurone involvement and its consequences, such as primary denervation and compensatory reinnervation of muscle fibres. However, it is not useful for the evaluation of the number of motor units. In neurogenic processes such as amyotrophic lateral sclerosis (ALS), abnormal needle EMG recording reflects the effects of two overlapping processes that occur in the muscles: acute denervation and reinnervation. In the initial stage of the disease, the loss of anterior horn cells results in acute motor fibre denervation. Afterwards, in the stage of secondary muscle fibre innervation, this denervation is compensated by sprouting axonal collaterals from surviving motor units into denervated muscle fibres. Routinely, the concentric needle electrode used in EMG records the combined action potentials generated by several fibres within a motor unit territory of 5–15 mm. This is known as the motor unit activity potential, or MUAP). MUAP parameters are increased in the stage of secondary reinnervation. This occurs due to an enlarged motor unit area and dispersion, which results from differences in the duration of potential components caused by abnormal neuromuscular transmission in immature axonal collaterals. Finally, in the stage of decompensation, MUAP parameters decrease due to continuous loss of motor units and a decrease in their area. Neurophysiological changes in motor units in ALS undergo continuous evolution along with a dynamic reorganisation.

Due to these overlapping processes, MUAP parameters do not appear to correlate with clinical muscle dysfunction. Pseudo-normal MUAP parameters may be observed even in the terminal stage of the disease, because MUAP parameters do not reflect the motor unit number but rather the effect of the denervation-reinnervation processes.

It is worth pointing out that conventional EMG abnormalities reveal denervation and reinnervation changes caused by lower motor neurone degeneration, but do not reflect the actual motor unit number.

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Motor unit number estimation

The importance of the motor unit as a crucial element in the production of force and movement was first recognised by Sherrington [1]. Subsequently, numerous studies have dealt with the structure and function of motor units. Studies on the methods estimating the number of motor units in individual muscles are still needed because there is a need for a valid biomarker to assess disease progression and to estimate potential treatment effects.

In 1971, McComas et al. described an attractively simple method for counting motor units. Recording from the extensor digitorum brevis, the authors maximally stimulated the deep peroneal nerve at the ankle and obtained a maximal compound motor action potential (CMAP) [2].

Then, starting from subthreshold stimulation levels, they gradually increased stimulus intensity until a quantal response was seen, representing the first motor unit activated. With further stimulus intensity increases, quantal increases in the response were recorded. Up to 11 discrete increments were recorded, with each increment assumed to represent the addition of one motor unit. The amplitude of the resultant response was divided by the number of increments to yield an estimate of the amplitude of a single unit; this value was divided by the maximum CMAP to give the estimate of the number of motor units. The incremental motor unit number estimation (MUNE) technique was soon applied to upper extremity muscles supplied by median, ulnar and radial nerves [3–5].

MUNE techniques have been used to quantify the proportion of surviving lower motor neurones in ALS. The results of multiple studies have confirmed that MUNE, when applied longitudinally, may reflect the rate of disease progression [6–9].

Assuming that the maximal CMAP is the sum of all single motor unit potentials, the universal rule for MUNE with incremental stimulation is that MUNE may be calculated as a ratio: the average size of a surface-detected single motor unit action potential (SMUP) should be divided by the maximum CMAP. SMUP is acquired by averaging several potentials of an increased amplitude with stimulation of an increasing intensity using the 'all or none' method.

Many techniques for estimating the average amplitude of single motor units have been suggested, but most have been limited by sampling bias and/or a lack of reproducibility. Different techniques for MUNE have been practiced, among them the spike-triggering averaging method using a voluntary muscle contraction to activate the motor unit, and the multiple point stimulation method with stimulation at multiple sites along the nerve.

One of the MUNE methods, with incremental stimulation in Shefner's modification, starts by obtaining CMAP in the most distal point with a maximal amplitude using supramaximal stimuli. During the second step of the test, the stimulating electrode is positioned in the following three locations: at the wrist crease; 4 cm proximal to the wrist crease; and in the cubital fossa [6, 10]. A standard three-site motor conduction programme is used with traces set to superimpose.

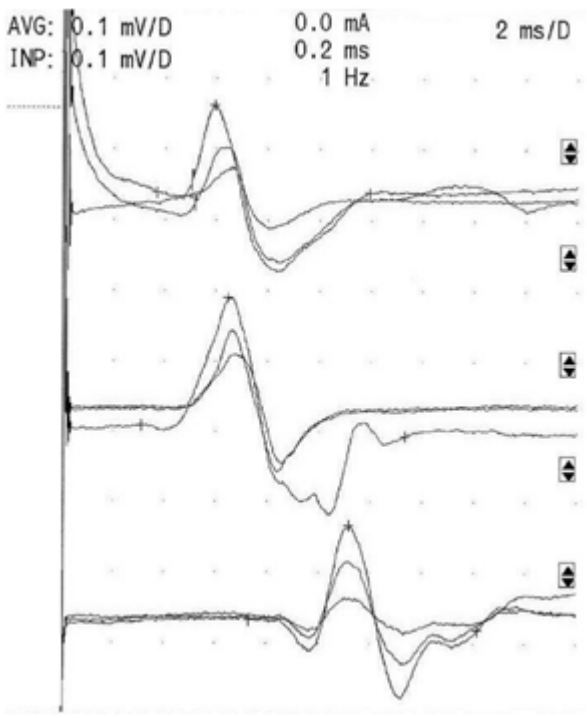

Figure 1. The second step in MUNE calculation: Three incremental responses in three sites of stimulations of the ulnar nerve (motor potentials)

Then, subthreshold stimuli are applied at the rate of 1/s, with stimulus intensity slightly increased until an 'all or none' response is recorded. For both initial and incremental responses, the minimum negative peak amplitude considered to be acceptable for recording is 25 μV. When the initial response has been obtained, two more incremental responses (of more than 25 μV) are recorded. Stimulus location is then moved to the second and third sites, and the same procedure of incremental stimulation is repeated [8] (Fig. 1).

The amplitude of three maximal responses from the three sites is totalled and divided by 9 to obtain the mean amplitude of an average surface-detected SMUP. The maximum CMAP amplitude is then divided by the SMUP amplitude to calculate the number of motor units [6, 10].

From the practical point of view, MUNE has some advantages. For example, it is not invasive and it is not unpleasant for the patient because only CMAP is obtained with a supramaximal impulse, and subsequent responses for a single motor unit are obtained with a very low current. For MUNE, cooperation with the patient is not required, so it can be used even in small children [11]. However, MUNE also has the disadvantage that it is useful only for the distal muscles. Due to response variability, extensive experience is needed to ensure that the proper curve is selected and the result is valid. Opinions have been voiced that the traditional

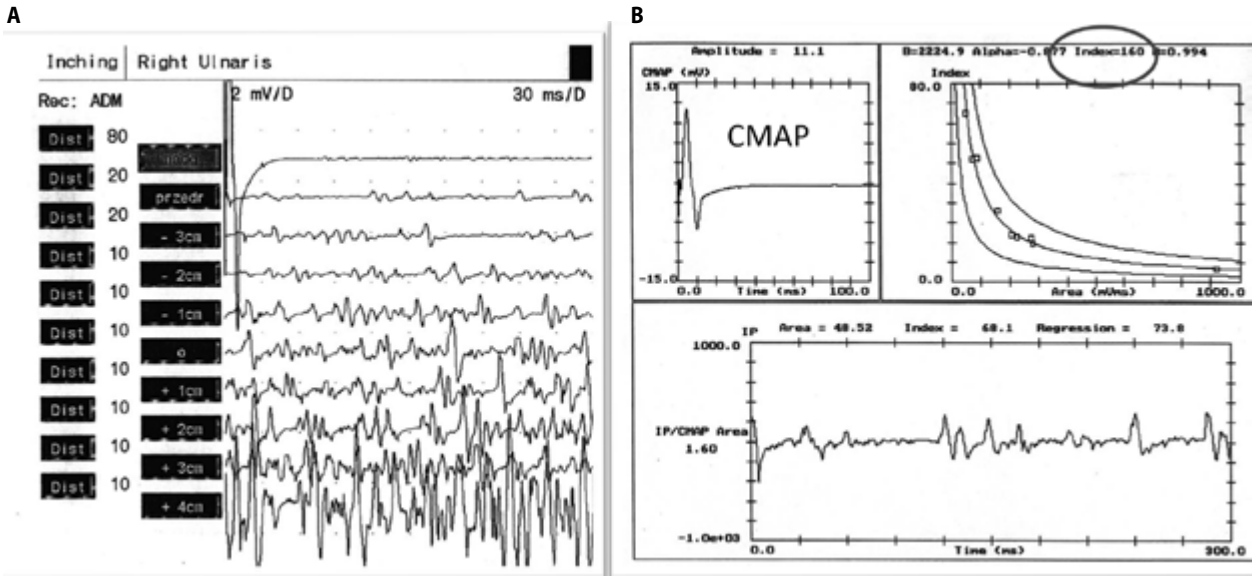

Figure 2 **A.** The surface electromyography interference pattern (SIP) of abductor digiti minimi is recorded when the patient maintains a constant isometric force of contraction at different force levels. This is used in conjunction with the CMAP to compute the so-called 'ideal case motor unit count (ICMUC)'. **B.** A plot of ICMUC versus SIP area is made, and the relationship of data points is modelled as a power regression equation and the MUNIX is calculated (from the own archives of EMG Laboratory) [14]

stimulation-based MUNE techniques are technically challenging, time consuming, and potentially limited by motor unit instability [12–13].

For these reasons, a surface-based electromyography MUNE technique that does not require nerve stimulation, something that has been termed the motor unit number index (MUNIX), has been developed in order to overcome some of the limitations of the MUNE method [13].

Motor unit number index

The MUNIX method is one of the recently developed electrophysiological approaches which may provide information about the degree of motor unit loss[14]. The MUNIX technique is a means of expressing the number of active motor units in a muscle as an index, rather than providing a direct measure of their total number [15].

MUNIX is a non-invasive method that can be applied to any muscle in which CMAP can be evoked by supramaximal nerve stimulation. The result of the examination is directly related to the number of functioning motor neurones in a given muscle. MUNIX uses a mathematical model based on CMAP and the surface interference pattern (SIP) following their import into an analysis software created by Nandedkar et al. [14, 16].

In the first step of MUNIX, a supramaximal CMAP is obtained by a standard tendon belly application of the surface electrodes to optimise the amplitude of the motor potential. Because obtaining maximal CMAP is crucial for the MUNIX result, it is recommended to reposition the recording electrode up to 5 times in order to record an optimised CMAP [17–18].

The next step is EMG signal recording during voluntary effort. The patient activates the examined muscle by resisting the examiner in an isometric contraction. It is recommended to avoid isotonic contraction and limb movement. The EMG signals should have spikes with an amplitude of 200 μV or more. The force is increased from minimal to maximal in 5–9 steps. At each force level, the patient maintains a steady contraction while SIP is recorded. The area and power of the CMAP and SIP are used to calculate the ideal case motor unit count (ICMUC). The MUNIX results are calculated using an automated method. The result is presented as a plot and a numeric value reflecting the number and size of motor units recruited at various force levels [18] (Fig. 2A, B).

Just as in MUNE with the incremental stimulation method, a strong correlation between CMAP amplitude and MUNIX in healthy controls has been found (Fig. 3). However, recurrent stimuli could result in habituation and a decreased potential amplitude, and thus intervals between the stimuli are required. A lower, underestimated CMAP amplitude has a dramatic effect on the reduction of MUNIX. When a potential is recorded with a stimulus artifact, the power cannot be measured accurately. Due to the need to perform a gradual effort, a good cooperation with the patient is crucial.

Our results suggest that MUNIX is a method that could be useful not only for the estimation of disease progression but also as a complementary method for the initial assessment of muscle [19]. From a practical point of view, the global MUNIX seems to be more useful for general patient assessment.

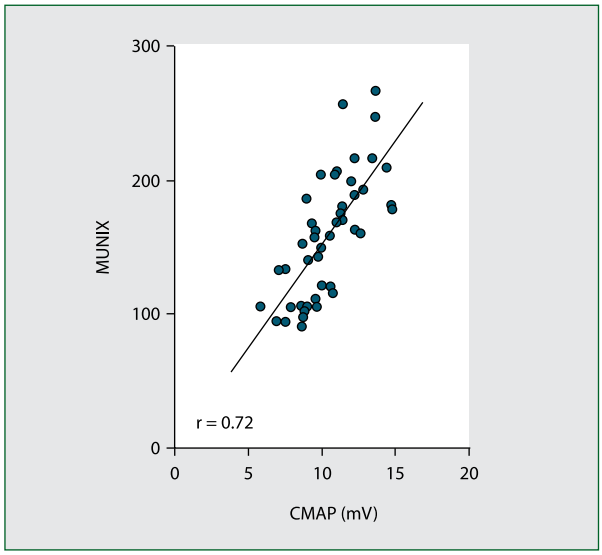

Figure 3. A strong correlation was found between CMAP amplitude and MUNIX results in healthy controls [14]

Use of MUNIX in amyotropic lateral sclerosis and other neurogenic processes

Amyotrophic lateral sclerosis is an adult-onset, progressive lethal neurodegenerative disorder characterised by a selective dysfunction and loss of upper and lower motor neurones. It leads to quadriplegia and respiratory insufficiency within a few years from the onset of initial symptoms. ALS shows a characteristic variability of onset and rate of disease progression which, together with a clinical heterogeneity, makes quantification of the symptoms problematic. It is therefore important to develop strategies that would allow objective assessment of the disease progression and the prediction of outcomes. The diagnosis of ALS is based on a clinical evaluation together with conventional EMG [20–21].

Amyotrophic lateral sclerosis

The reliability and sensitivity of MUNIX as a tool to monitor the progression of motor unit loss during the course of the disease in ALS patients has been reported in many studies. Some of them focused only on a single muscle. In the study by Boekestein, the MUNIX and HD-MUNE (high density MUNE) of the thenar muscle was evaluated. Patients with ALS were assessed at baseline, within two weeks, and after four and eight months. There was a significant positive correlation between MUNE and MUNIX values in ALS patients. After eight months, both MUNE and MUNIX values in the ALS patients had decreased significantly more compared to the Medical Research Council (MRC) scale, ALS functional rating scale (ALSFRS), and CMAP ($p < 0.05$) [22].

In the study by Fathi, MUNIX was recorded in the abductor pollicis brevis and tibialis anterior muscles bilaterally in ALS patients, with two measurements, one at the first visit and the second at a follow-up visit. The consistency of reproducibility of MUNIX in 30 ALS patients during the course of the disorder was analysed. A significant correlation between the first and the second MUNIX measurement in all tested muscles was found. A statistically significant good reproducibility of MUNIX in all four measured muscles was obtained at the follow-up visit [23].

Even more valuable are studies with several MUNIX examinations assessing disease progress and with evaluation of the distal as well as proximal muscles.

In a large clinical trial (27 centres participating in the Biogen study, 792 individual test-retest measurements), MUNIX was measured in a set of six muscles: the abductor pollicis brevis, abductor digiti minimi, first dorsal interosseous, biceps brachii, tibialis anterior, and extensor digitorum brevis. The aim was to analyse the reliability of MUNIX measurements and possible pitfalls in implementing the method in clinical trials. Mean coefficient of variation (COV) of all raters at the first measurements was 12.9% ± 13.5% (median 8.7%). The need for repeated tests ranged from 0 to 43 (mean 10.7 ± 9.1, median 8). The biceps brachii muscles showed the highest repetition rates. Evaluation of the biceps brachii failed in approximately two thirds of cases due to contamination of the CMAP by co-stimulation of other nearby nerves, such as the musculocutaneous nerve, with volume conducted signals from wrist and finger flexors or even the triceps muscle. MUNIX variability correlated considerably with the variability of CMAP. The authors concluded that MUNIX showed generally good reliability, but was rater-dependent and that ongoing support for the raters was needed [24].

Neuwirth et al. reported the rate of MUNIX decline in ALS during a series of examinations at three-month intervals after the diagnosis. Three centres measured MUNIX in 49 ALS patients every three months in six muscles (abductor pollicis brevis, abductor digiti minimi, biceps brachii, tibialis anterior, extensor digitorum brevis, and abductor hallucis) on the less affected side. The decline in MUNIX in initially non-wasted, clinically strong muscles (manual muscle testing, MMT grade 5) was analysed before and after the onset of weakness. The average monthly relative MUNIX loss was 5.0% before, and 5.6% after, the onset of weakness. Although the preclinical loss of motor units is a well-known feature of ALS and can be detected by needle EMG very early in the course of the disease even in a clinically normal muscle, MUNIX seems to be a valuable measurable marker of preclinical abnormalities. In that study, the rate of MUNIX change was significantly higher compared to the ALS functional rating scale ALSFRS and CMAP change over 12 months prior to the onset of muscle weakness. This makes MUNIX a good

biomarker candidate for disease progression, and possibly pharmacodynamic response [25].

In one of our studies, we analysed MUNIX in ALS patients (15 patients) and we found a significant correlation between the global MUNIX score and the clinical dysfunction as measured by the ALSFRS-R scale ($P < 0.05$). The global MUNIX score showed a higher monthly decline (4.3%) compared to ALFRS-R (0.7%) and the MRC global score (0.5%). This study also confirmed that the MUNIX method is a sensitive, reliable, and accurate tool reflecting both motor dysfunction and disease progression in ALS. We have found this approach to be more reliable and technically easier in distal muscles with less atrophy and a better strength.

The results of our study suggest that MUNIX is a method that may be useful not only for estimation of disease progression but also as a complementary method for initial muscle assessment. We also made some practical observations. The MUNIX method may be affected by an inappropriate CMAP recording caused by technical or anatomical problems. It is crucial to find the optimal location of the recording electrode, and to repeat CMAP recording to ensure that the motor response with a maximal amplitude is obtained. A lower, underestimated CMAP amplitude has a dramatic effect on the reduction of MUNIX. When a potential is recorded with a stimulus artifact, the power cannot be measured accurately and the same problem affects MUNIX too [19].

To date, the usefulness of this method for assessing the dynamics of disease-related changes has been studied mainly in non-treated subjects. One of the most recent studies focused on choosing an optimal monitoring tool after intraspinal transplantation of adipose tissue-derived regenerative cells in three patients with amyotrophic lateral sclerosis. The treatment did not prove effective in terms of reversing or delaying disease progression, but a number of observations were made. Of all methods used, MUNIX proved to be the first and the most sensitive tool for identifying fine changes at the muscle level. It was markedly more sensitive than ALSFRS R and MRC. In that study, dynamometry was the closest measurement to MUNIX both in the upper and the lower limb [26].

Spinal muscular atrophy

In one of the most recent studies, hand muscle innervation pattern was studied by the MUNIX method in 38 adult patients with genetically confirmed 5q spinal muscular atrophy (SMA). Data was compared to that of healthy controls and ALS patients and correlated with typical disease-relevant scores and other clinical and demographic characteristics. By calculation of the MUNIX ratios, the authors identified a specific hand muscle wasting pattern for SMA which is different to the split hand in ALS. MUNIX parameters strongly correlated with established disease course parameters, independently of disease stages [27].

Polyneuropathy

The MUNIX technique was also assessed unilaterally in the abductor digiti minimi, the abductor pollicis brevis, and the tibialis anterior muscles in 14 patients with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) on two different occasions by two blinded examiners, and the MUNIX score was calculated by adding the results for the abductor digiti minimi, the abductor pollicis brevis, and the tibialis anterior muscles. The intraclass correlation coefficient (ICC) was high for inter- and intravariability for all three examined muscles, and the combined MUNIX scores from the first and the second evaluations were strongly correlated to each other. The MUNIX score was significantly correlated with MRC testing and also with the overall neuropathy limitation scale and the Rasch-built overall disability scale. The authors concluded that the MUNIX technique estimates the axonal loss and the number of functional motor units and that the MUNIX score may be a good instrument to evaluate CIDP patients during their follow-up [28].

In one study, a short-term effect of intravenous immunoglobulins (IVIg) in multifocal motor neuropathy (MMN) was evaluated using MUNIX. MUNIX was assessed longitudinally in seven MMN patients and 17 healthy controls in the abductor pollicis brevis and abductor digiti minimi muscles. All MMN patients were evaluated on the first day of IVIg infusion, five MMN patients were evaluated 22 days after IVIg infusion, and three MMN patients were evaluated one month after two IVIg infusions. The authors concluded that MUNIX seems to be a reliable and sensitive tool for monitoring the short-term efficacy of IVIg in MMN [29].

MUNE or MUNIX

Interestingly, in the study by Higashihara, evaluation by MUNE with multipoint stimulation and MUNIX was performed in 15 healthy subjects at three different time-points by the same examiner. ICC and COV values for MUNIX and MUNE were excellent across the three tests (0.80 and 0.77, respectively), although COV values were significantly lower for MUNIX than for MUNE ($P < 0.01$). In addition, the test-retest reproducibility was better for MUNIX, a finding largely attributable to poor reproducibility of the single motor unit action potential area. The authors concluded that MUNIX demonstrated better intra-rater reproducibility and may be a more reliable neurophysiological biomarker than MUNE [30].

In conclusion, MUNIX seems to be valuable tool for monitoring the progression of diseases with neurogenic processes. While multiple studies have confirmed the usefulness of MUNIX for monitoring ALS progression, the application of MUNIX in other diseases with lower motor neurone degeneration needs further assessment.

MUNIX is recommended because it shows good repeatability, is less time-consuming, can be used for both distal and proximal muscles, and requires less electrical stimulation. However, currently there are only few pharmacological studies using MUNIX which would test the utility of this approach. MUNE with incremental stimulation can be recommended for the distal muscles, and for those occasions when there is no possibility of patient cooperation. The crucial issue regarding the application of both MUNIX and MUNE is the electromyographist's experience and his or her attention to some very important technical aspects.

Ethics committee approval was not necessary for preparation of this article.

The author reports no sources of funding.

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RESEARCH PAPER

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2019, Volume 53, no. 4, pages: 258–264
DOI: 10.5603/PJNNS.a2019.0028

ISSN 0028–3843

Assessment of the relationship between platelet reactivity, vascular risk factors and gender in cerebral ischaemia patients

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ABSTRACT

Aim. Excessive activation and platelet aggregation play important roles in the aetiopathogenesis of cerebral ischaemia. The aim of this study was to assess the relationship between platelet reactivity, gender and vascular risk factors in cerebral ischaemia patients.

Clinical rationale for the study. The research is useful because we found high risk groups of inefficient aspirin treatment in cerebral ischaemia patients.

Material and methods. The study involved 101 patients, including 69 patients with ischaemic stroke and 32 patients with transient ischaemic attack. The assessment of platelet reactivity was made within 24 hours of the disease onset using two aggregometric methods: impedance and optical.

Results. Resistance to acetylsalicylic acid among people with cerebral ischaemia was estimated at 30.69% using impedance aggregometry and 9.2% using optical aggregometry. There were no differences in platelet reactivity or ASA resistance between the groups of patients with stroke and TIA in either method. In the whole group of patients ($p = 0.04$), and in the group of patients with stroke ($p = 0.0143$), higher reactivity of platelets was observed by impedance aggregometry in men than in women. In the whole group of patients ($p = 0.0229$), and in the subgroup with stroke ($p = 0.0123$), it was shown that aspirin resistance is significantly more common in the subgroup of men than in women. In patients suffering from nicotine addiction, significantly higher platelet reactivity was found in the whole group of patients ($p = 0.004$), as well as in the subgroup of patients with stroke ($p = 0.0135$).

Conclusions. There are no differences between platelet reactivity and the incidence of aspirin resistance in patients with stroke and TIA. Male gender and smoking are associated with greater reactivity of platelets and more frequent occurrence of acetylsalicylic acid resistance in patients with cerebral ischaemia.

Clinical implications. Dual antiplatelet therapy or clopidogrel treatment should be considered in smoking males with cerebral ischaemia due to the high risk of aspirin inefficiency.

Key words: platelet reactivity, stroke, aspirin resistance, gender, risk factors

(*Neurol Neurochir Pol 2019; 53 (4): 258–264*)

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Introduction

Stroke is a crucial social and medical problem of the 21st century, and one of the main causes of morbidity and long-term disability. It is also the second most frequent cause of death in the world [1]. In 2013 the American Heart Association/American Stroke Association (AHA/ASA) proposed a new definition of ischaemic stroke as an episode of sudden neurological disorder caused by focal cerebral, spinal cord or retinal ischaemia persisting over 24 hours or corresponding to the morphological features of central nervous system ischaemia. Thus, due to such an updated definition, ischaemic stroke can also be diagnosed when clinical symptoms last less than 24 hours but where neuroimaging studies have demonstrated an ischaemic infarction, as well as in thrombolytic patients whose symptoms of focal deficit have undergone a rapid regression [2]. If the time and radiology criteria are not met, transient ischaemic attack (TIA) is diagnosed.

Platelet activation plays an important role in the pathomechanism of ischaemic stroke, especially in the thrombotic mechanism. Antiplatelet therapy, by inhibiting the activation and aggregation of platelets, is the current standard of pharmacological treatment, both in the treatment of the acute phase and in the prophylactic treatment of secondary ischaemic stroke [3]. Both European and American standards recommend several antiplatelet drugs with similar efficacy, but acetylsalicylic acid (ASA) is still the most commonly used. Unfortunately, a phenomenon that limits the effectiveness of ASA is the so-called resistance to acetylsalicylic acid [4]. In order to optimise antiplatelet therapy, tests evaluating platelet function-platelet reactivity are used, and these form the basis for the diagnosis of laboratory resistance. Obtaining high values of platelet reactivity indicates a weak therapeutic effect on the anti-aggregation drug [5].

Previous reports in the literature regarding the occurrence and importance of aspirin resistance in patients with cerebral ischaemia are scarce and have had inconclusive results. Therefore, the aim of this study was to assess the relationship between platelet reactivity, vascular risk factors and gender in patients with cerebral ischaemia.

Clinical rationale for the study

The results of this study will be clinically useful, because we found high risk groups of aspirin treatment inefficiency in patients with cerebral ischaemia and were able to offer them a different, more effective, prophylaxis.

Material and methods

Research population

The study was conducted between February and December 2016 in the Department of Neurology at the University Hospital No. 1 in Bydgoszcz. The prospective study included 69 patients who met the criteria for the diagnosis of ischaemic stroke and 32 patents with TIA. On admission oral treatment with acetylsalicylic acid (ASA) at a dose of 150 mg was commenced in all patients. The following exclusion criteria were used: lack of patient consent to participate in the study, or inability to express it consciously (e.g. stroke with aphasia or quantitative disturbances of consciousness), patients with embolic cerebral ischaemia (with documented atrial fibrillation, thrombus in the heart cavities or dilated cardiomyopathy), patients with oncological history, patients who had taken ASA before admission, patients with chronic inflammatory processes that may affect the objective assessment of platelet function, e.g. with chronic venous thrombosis of the lower limbs or chronic lower limb ischaemia, patients who had had a stroke or TIA during the previous two years, patients with significant bleeding in the last two years, e.g. gastrointestinal bleeding, thrombocytopenia < 100,000/ul, level of haemoglobin <9 g/dL, value of haematocrit < 35%. The general characteristics of the studied population and a comparison between the group of patients with stroke and those with TIA are set out in Table 1. The study protocol was approved by the Bioethics Committee of Nicolaus Copernicus University in Torun at Collegium Medicum of Ludwik Rydygier in Bydgoszcz (KB number 73/2016). This study included only patients who, having read the study protocol, signed informed consent to participate in the study.

Platelet reactivity research

The study of platelet reactivity was performed by optical aggregometry and impedance aggregometry in the Laboratory of Biotechnology of the Chair of Pharmacology and Therapy at Collegium Medicum in Bydgoszcz of UMK in Torun. Patients' blood tests to assess platelet reactivity were performed at a similar time of day (10am–12noon) within 24 hours of stroke symptoms onset. The optical aggregometry (LTA, light transmission aggregometry) test was performed using a Chrono-Log aggregometer (Havertown, PA, USA). Arachidonic acid was used as the agonist. The aggregometer analysed changes in transmitted light in percentages, with 0% being the maximum optical density of platelet rich plasma and 100% a complete lack of plasma optical density. Then, the signal was automatically converted to area under the curve (AUC) units — as the final result of the determination. An average increase in absorbance of more than 20% (or AUC > 115) was considered to be resistance to ASA that is equivalent to that of 'high' on aspirin treatment platelet reactivity induced by arachidonic acid. The test was performed according to the standard protocol [6]. The evaluation of optical aggregometry was performed in 65 of the 101 subjects, due to an aggregometer failure that could not be repaired during the study.

The study of platelet function by impedance aggregometry was performed using a Multiplate- Dynabyte multi-channel platelet function analyser (Roche Diagnostics, France). The study used the so-called ASPI test, i.e. aggregation dependent on

Table 1. Comparison of selected risk factors, anthropometric and biochemical parameters obtained in patients with stroke and TIA

Parameter	Stroke N = 69	TIA N = 32	P-values
Age median (range)*	67 (40–89)	70 (49–90)	0.1556
Male N, (%)**	35 (50.7%)	13 (40.6%)	0.3444
Hypertension N, (%)**	61 (88.4%)	26 (81.25%)	0.3628
Diabetes N, (%)**	25 (36.3%)	11 (34.3%)	1.0
Hyperlipidemia N, (%)**	28 (40.6%)	17 (53.12%)	0.2846
Smoking N, (%)**	24 (34.8%)	6 (18.75%)	0.1593
Ischaemic heart disease N, (%)**	9 (13.0%)	4 (12.5%)	1.0
Obesity N, (%)**	48 (69.5%)	22 (68.75%)	0.7675
CRP [mg/L] Median (range)*	4.79 (0.36–30.45)	1.835 (0.21–15.2)	0.5157
HBA1c [%] Median, (range)*	318 (59–590)	292.5 (168–469)	0.1864
Homocystein [µmol/L] Median (range)*	5,7 (5–10.04)	5.8 (4.2–7.5)	0.2713
Fibrinogen [mg/dL] Median (range)*	10.78 (3.52–48.6)	9.75 (5.88–18)	0.3524

*Mann-Whitney U-test; ** Chi^2 calculation

cyclooxygenase — using arachidonic acid as a platelet activator. Aggregation results were obtained after another 6 minutes for each test as an average of two measurements in the form of a curve, on the basis of which the area under the curve (AUC) was determined. The AUC parameter was reported as the final result of the determination. Those patients with results above 40 AUC were considered to be ASA resistant, that is equivalent to 'high' on aspirin treatment platelet reactivity induced by arachidonic acid. Patients with AUC values under 30 were treated as sensitive to ASA, and those measured as being from 30 to 40 as mildly sensitive to ASA. The test was performed according to the standard protocol [7]. The evaluation of impedance aggregometry was performed in all 101 subjects.

Statistical evaluation methods

The statistical analysis of collected data was performed with the help of STATISTICA statistical program — version 13.1, Dell. Compatibility with normal distribution was tested with the Shapiro-Wilk test and homogeneity of variance with the Levene test. Due to the incompatibility of the distribution of features with the normal distribution and the lack of homogeneity of variance in the analysis, non-parametric tests were used — U Mann–Whitney test (assessment of the relation between binary and continuous variables), Spearman's rank correlation test (evaluation of the relations between variables), and chi-square independence test (evaluation of relations between categorised variables). A significance level of $p < 0.05$ was considered statistically significant.

Results

Assessment of platelet reactivity

The assessment of platelet reactivity with LTA was performed in 65 patients: in the group of 43 stroke patients, the median was 8.8 AUC (min. 0 AUC, max. 208.6 AUC), while in 22 TIA patients the median was 8.25 AUC (min. 0.2 AUC, max. 278 AUC). There was no statistically significant difference in platelet reactivity between the study group of stroke patients and the TIA group ($p = 0.9558$). The incidence of aspirin resistance in all patients was 9.2%.

Evaluation of platelet reactivity with the Multiplate system was performed in 101 patients. The median of platelet reactivity in the whole group was 27 AUC (min. 6 AUC, max. 108 AUC). In the group of stroke patients, the median was 29 AUC (min. 6 AUC, max. 108 AUC), while in the TIA group the median was 24 AUC (min. 7 AUC, max. 108 AUC). There were no statistically significant differences in platelet reactivity between the study group of stroke patients and the TIA group ($p = 0.8667$). Using the criterion of ASA resistance to the ASA-resistant group (AUC > 40), 31 patients were included, 16 patients were included into the group with medium ASA-sensitivity ($30 \leq AUC \leq 40$), and 54 to the ASA-sensitive group (AUC < 30). The distribution of the occurrence of aspirin resistance in patients with stroke and TIA did not differ in a statistically significant way (Chi^2 NW = 0.17; $p = 0.9185$) (Fig. 1). The incidence of resistance to ASA in the Multiplate study was 30.69% in all patients with ischaemia of the brain; in the subgroup of patients with stroke it was 31.9%, and in the subgroup with TIA it was 28.1%.

Platelet reactivity and anthropometric parameters

There was no significant correlation between the age of the patients and platelet reactivity assessed with the Multiplate or the LTA method ($R = -0.1499$, $p = 0.3451$ for Multiplate and $R = 0.05$ and $p = 0.6585$ for LTA). In the whole group of subjects, statistically higher platelet reactivity was assessed by means of the Multiplate test in men than in women (median, respectively: 34.5 vs 23 AUC; $p = 0.04$) (Fig. 2). A similar difference was also found in the subgroup of patients with stroke

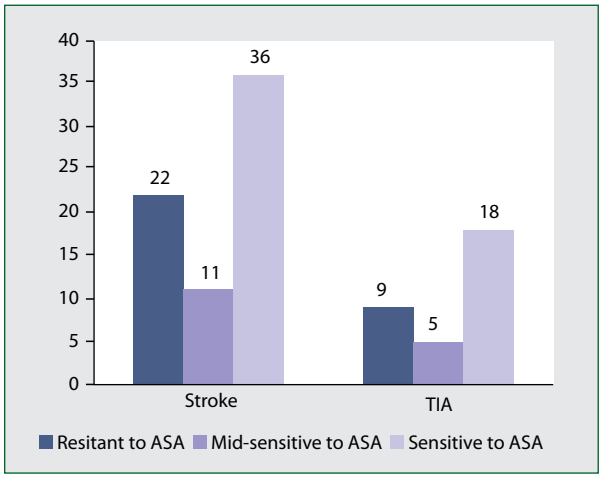

Figure 1. Distribution of the occurrence of aspirin resistance in patients with stroke and TIA

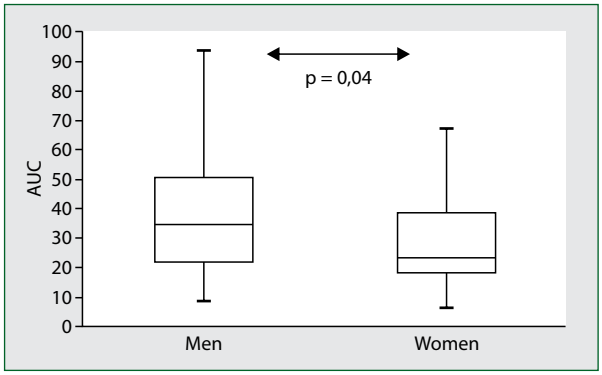

Figure 2. Comparison of platelet reactivity by impedance aggregometry (in AUC-units) in men and women with cerebral ischaemia

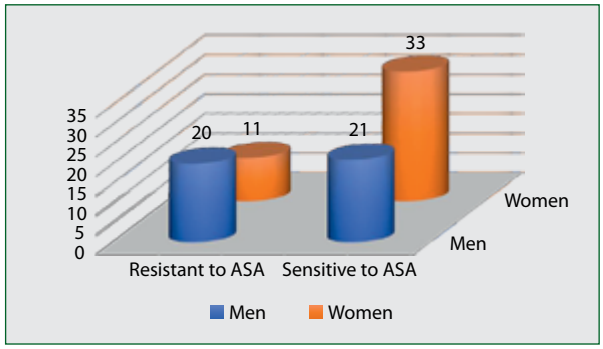

Figure 3. Occurrence of ASA resistance in men and women with cerebral ischaemia

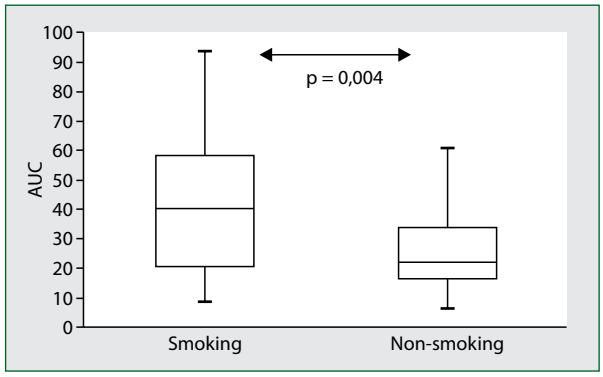

Figure 4. Comparison of platelet reactivity by impedance aggregometry (in AUC-units) in smoking and non-smoking patients with cerebral ischaemia

(median, respectively: 40 vs 23.5 AUC, p = 0.0143). In the subgroup of patients with TIA, similar relationships were not demonstrated (p = 0.7443). There was no relationship between platelet reactivity assessed by the LTA test and patient gender (in the whole group p = 0.6841, in the subgroup with stroke p = 0.6270, in the subgroup with TIA p = 0.8030). In the whole group of patients, it was demonstrated that aspirin resistance was significantly more common in the subgroup of men than in women (Chi^2 NW = 5.18; p = 0.0229) (Fig. 3). A similar relationship, statistically significant, was noted in the subgroup of patients with stroke (Chi^2 NW = 6.26; p=0.0123). In the subgroup of patients with TIA, there were no such relationships (Chi^2 NW = 0.08; p = 0.78).

Platelet reactivity and risk factors for vascular disease

In patients suffering from nicotine addiction, significantly higher platelet reactivity was found, assessed by the Multiplate method, both in stroke and TIA patients (p = 0.004) (Fig. 4), as well as in the subgroup of patients with stroke (p = 0.0135) There was no effect of smoking on the platelet reactivity assessed by LTA. Other risk factors for vascular disease did not have a significant impact on platelet reactivity, as assessed by the Multiplate method (Tab. 2) and the LTA method. In the group of patients with ischaemic stroke burdened with nicotine addiction, there was a significantly higher proportion of ASA-resistant patients compared to non-smokers (Chi^2 NW = 10.1592; p = 0.0014) (Fig. 5).

Discussion

The evaluation of the impact of recognised risk factors for vascular disease on platelet reactivity has been the subject of many studies and publications. Independent authors have not shown, in their studies, a relationship between the occurrence of hypertension, diabetes, hyperlipidaemia or ischaemic heart disease and the level of platelet reactivity, using various methods of assessing platelet function [8–12]. Only El-Mitwalli et al. [13] reported that hyperlipidaemia is more common in an ASA-resistant group. In this study, a significant relationship between platelet reactivity and hypertension, coronary artery

Table 2. Comparison of platelet reactivity assessed by the Multiplate method (in AUC-units) in subgroups of patients with stroke with and without current given risk factor

Risk factor	Multiplate		P-values
	Risk factor present Median (range)	Risk factor absent Median (range)	
Hypertension	24.5 (6–87) AUC	29 (9–108) AUC	0.7800
Diabetes	29 (6–108) AUC	27 (9–79) AUC	0.6521
Hyperlipidemia	28 (6–87) AUC	30.5 (9–108) AUC	0.7848
Ischaemic heart disease	30 (6–108) AUC	17 (6–69) AUC	0.1077
Smoking	24 (6–108) AUC	40.5 (10–87) AUC	**0.0135**
Obesity	40 (6–87) AUC	27 (9–108) AUC	0.2420

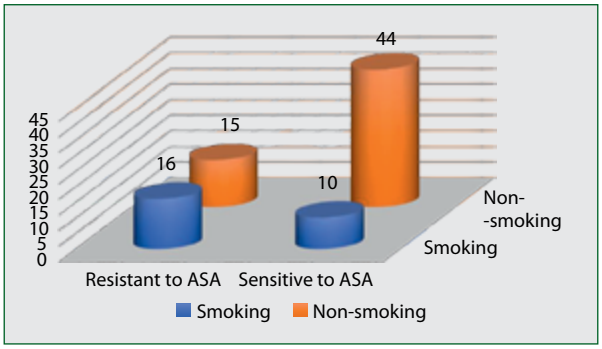

Figure 5. Occurrence of ASA resistance in subgroups of patients with cerebral ischaemia withand without nicotine addiction

disease, diabetes and hyperlipidaemia was also not shown, which coincides with the observations of most authors.

The risk factor that significantly differentiated the reactivity of platelets in this study was nicotine addiction. Active tobacco smokers were characterised by a higher median platelet reactivity than non-smokers. In addition, the incidence of nicotine addiction in the group of patients with cerebral ischaemia in the ASA-resistant group was significantly higher than in the ASA-sensitive group. Zheng et al. [12] also showed in their study that nicotine addiction is more common in patients with stroke in the ASA-resistant patients than those sensitive to ASA ($p = 0.02$); similar relationships were noted by El-Mitwalli et al. Other authors have not found a relationship between nicotine addiction and platelet reactivity or ASA resistance in patients with ischaemic stroke [8–11,14]. Smoking affects the functions of platelets in a multifactorial manner. Nicotine addiction intensifies platelet aggregation, and also reduces their sensitivity to exogenous NO (nitric oxide), thereby increasing their adhesion and activation [15]. Smoking three cigarettes quickly in a row increases the ADP-dependent platelet aggregation *in vitro*. Smoking also activates the expression of P-selectin on the surface of platelets and its serum level, which stimulates platelet activation. In addition, regardless of the mechanisms leading to the modification of platelet function, smoking cigarettes increases blood viscosity, the activity of coagulation processes, fibrinogen levels and blood pressure, and reduces cerebral blood flow through vasospasm. Nicotine addiction raises the risk of stroke on average by 1.5–3 times [16]. All patients after stroke or TIA are advised to stop smoking, including avoiding passive smoking. With regard to the results of this work, this recommendation proves to be a necessary requirement to obtain effective antiplatelet therapy. The American and European guidelines do not give information about the routine determination of platelet reactivity which points to a lack of antiplatelet therapy modifications in smokers. It is worth mentioning the work of Blache et al. [17] who showed that the increased reactivity of platelets is reduced to optimal limits only by a dose of 650 mg ASA. It is also worth noting the results of the work of Rollini et al. [18] who assessed platelet reactivity in patients with advanced atherosclerosis, who were taking ASA, and who were additionally given clopidogrel at a dose of 75 mg for 7–10 days, who then repeated platelet reactivity assessment. In the group of the greatest smokers, a significant decrease in platelet reactivity was achieved.

The presented results may suggest the necessity to adjust the doses of antiplatelet drugs in patients with nicotine addiction, the replacement of ASA with clopidogrel in patients with recurrent stroke, and even the consideration of dual antiplatelet therapy in smokers.

The results of the study showed higher platelet reactivity and a higher incidence of aspirin resistance in men compared to the whole group of subjects and compared to patients with stroke. Similar conclusions were drawn by Jaremo et al. [19], who in a population of men with ischaemic stroke had higher platelet activation assessed by the method of flow cytometry. However, the relation between platelet reactivity and gender remains debatable due to the fact that most other researchers have not shown any relationship between platelet reactivity and aspirin resistance in populations of patients with stroke [8, 9, 12, 20, 21].

In the analysis presented in this study, the groups of patients with stroke and TIA did not differ in terms of gender or platelet reactivity. Considering the abovementioned fact, the demonstration of a significant dependence of platelet

reactivity on gender in the whole group, and especially the significant gender relationship in the subgroup of patients with stroke, emphasises that male gender is an independent platelet activating factor in stroke patients. The explanation of the dependence of platelet activity on gender may be the hormonal basis, as it has been shown that testosterone increases platelet aggregation, while oestrogens and progesterone inhibit platelet aggregation [22, 23]. Greater platelet reactivity in the male gender may also partly explain why the incidence of stroke is lower in women and why stroke occurs in women at a later age [24, 25]. On the other hand, taking into account the greater aspirin resistance in the group of men noted in this study, women are also better beneficiaries of antiplatelet therapy than men, in whom greater resistance to ASA may result in a less effective anti-aggregatory effect of the drug. Similar observations were made by Becker et al. [26] who in their study showed that small doses of ASA (81 mg) more effectively inhibit platelet aggregation in women than in men, which corresponds to lower platelet reactivity found in women in the LTA and PFA (Platelet Function Assay) method — 100 after the ASA therapy. Although in the above study only healthy volunteers from a group at increased risk of cardiovascular incidents were evaluated, not a population of patients with stroke, its results may indirectly confirm the relationship between aspiring resistance and gender indicated in this study.

The current study has its limitations. The number of the studied population is moderate, but proved to be sufficient to formulate conclusions. Most conclusions were based only on the results of platelet reactivity by impedance aggregometry (Multiplate). The conclusions based only on one, poorly standardised, method, with agreed resistance criteria, should be approached with caution [27].

However, the authors consider the one-time assessment of platelet function to be the greatest limitation of their analysis, which was performed at different times after the onset of stroke symptoms within the first 24 hours and at different times from taking the dose of acetylsalicylic acid. It seems that an assessment of platelet function only in a single measurement may be insufficient to properly assess the effect of ASA resistance. Taking into account the data from the literature, the authors are of the opinion that only the sequential determination of platelet reactivity on successive days of stroke seems to be most optimal for the characterisation of aspirin resistance phenomenon [9, 21, 28]. Another limitation is the fact that laboratory resistance does not always correlate with clinical resistance [29, 30].

Conclusions

1. The prevalence of aspirin resistance in the group of patients with cerebral ischaemia is estimated at 30.69% in impedance aggregometry and 9.2% in optical aggregometry.
2. There are no differences between platelet reactivity and the incidence of aspirin resistance in patients with stroke and TIA.
3. Male gender and smoking are associated with greater reactivity of platelets, and more frequent occurrence of aspirin resistance, in patients with cerebral ischaemia.

Clinical implications

On the basis of this study it could be considered optional treatment in smoking males with cerebral ischaemia because of the high risk of aspirin inefficiency. A higher dose of aspirin, dual antiplatelet therapy, or clopidogrel treatment could be taken for this purpose, while bearing in mind the increased risk of bleeding complications. In smoking males, routine determination of platelet reactivity for evaluation of aspirin resistance should be considered, although this is still not available in many countries. Further studies on this subject are needed to confirm our observations.

Conflict of interest: *None declared.*
Financial suport: *This publication was prepared without any external sources of funding.*

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RESEARCH PAPER

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2019, Volume 53, no. 4, pages: 265–270
DOI: 10.5603/PJNNS.a2019.0027

ISSN 0028–3843

Clinical value of $^{99}Tc^{m}$-MIBI gated myocardial perfusion imaging in evaluating sarcoglycanopathy

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ABSTRACT

Aim. The purpose of this study was to analyse the diagnostic value of gated myocardial perfusion imaging (G-MPI) in the evaluation of myocardial injury in sarcoglycanopathy.

Materials and methods. Twenty-eight patients diagnosed with sarcoglycanopathy were evaluated using $^{99}Tc^{m}$-methoxyisobutylisonitrile($^{99}Tc^{m}$-MIBI) G-MPI. The data was processed into tomographic images, and the left ventricular function was analysed using quantitative gated SPECT (QGS) to assess the degree of impairment in myocardial and cardiac function.

Results. The images of 23 of the patients (82.1%) were positive. Two hundred and twenty-nine sub-segments with abnormal lesions were detected out of 391 cardiac sub-segments of these 23 positive cases. According to the segmental abnormalities, the cases were divided into two cases (8.7%) with single abnormal wall segment, six cases (26.1%) with two abnormal wall segments, and 15 cases (65.2%) with three or more abnormal wall segments or scattered lesions.

Conclusions. $^{99}Tc^{m}$-MIBI G-MPI can objectively show impaired myocardium in patients with sarcoglycanopathy. Therefore, this method is helpful for early diagnosis and follow-up of myocardial damage.

Key words: Sarcoglycanopathy, tomography, emission computer, single photon, MIBI

(*Neurol Neurochir Pol 2019; 53 (4): 265–270***)**

Introduction

Sarcoglycanopathy is the general term used to describe limb-girdle muscular dystrophy (LGMD) (2D, 2E, 2C, and 2F), which is caused due to defects in the expression of the four subunits of myosin protein: α-, b-, g-, and d [1, 2]. The coding genes for α-, b-, g-, and d subunits of myosin protein are SGCA(17q21), SGCB(4q12), SGCG(13q12), and SGCD(5q33), respectively. LGMD refers to a group of hereditary skeletal muscle diseases with the main clinical manifestations being amyosthenia and progressive aggravated myatrophy in the proximal extremity and lumbar muscles [3–5]. Both the myocardium and the skeletal muscles belong to the striated muscle, and they are differentiated from the mesenchymal cells. The mesenchymal cells first differentiate into the myoblasts, and then differentiate into the myocytes and the skeletal muscle cells differently [6]. Due to these common histologic and embryologic features, genetic or metabolic diseases that affect the skeletal muscle fibres may cause myocardial damage by affecting the structure, function, or metabolism of the cardiac muscle cells.

At present, studies on cardiac injury in sarcoglycanopathy are mostly focused on electrocardiograms or echocardiography. For example, ultrasound is used to measure the changes in thickness of the atrophied muscles [7], or to diagnose and evaluate the efficacy of myocardiac dystrophy [8]. The advantage of magnetic resonance imaging (MRI) is that it can access the energy metabolism and function of the heart, which is important information about the early stages of myocardial damage in muscular dystrophy [9]. Radionuclide myocardial imaging can simultaneously display myocardial metabolism and blood flow distribution. It is also used in determining the existence of myocardial ischaemia as well as the ischaemic site and scope, detecting myocardial survival, and understanding the wall movement and the left ventricular function [10]. However, few studies have been conducted into applying

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radionuclide myocardial imaging in evaluating myocardial damage in sarcoglycanopathy.

In this study, $^{99}Tc^{m}$-methoxyisobutylisonitrile ($^{99}Tc^{m}$-MIBI) gated myocardial perfusion imaging (G-MPI) was performed on 13 patients with myopathy (the CON group) and 28 patients with sarcoglycanopathy (the SAR group) diagnosed through clinical, routine pathological staining, and immunohistochemical staining of muscle biopsy in our hospital. The aim was to analyse the value of gated myocardial tomography in evaluating myocardial damage and heart function in patients with sarcoglycanopathy.

Materials and methods

Clinical data

Twenty-eight patients with sarcoglycanopathy diagnosed through clinical, routine pathological staining, and immunohistochemical staining of muscle biopsy in the Department of Neuromuscular Diseases of our hospital from September 2008 to July 2017 were enrolled in the study, including 17 males and 11 females, aged 8–30 years, with an average age of 15.3 ± 4.1 years. The CON group was composed of 13 patients, aged 16.5 ± 3.9 years. The diagnosis was based on the clinical manifestations of amyosthenia and progressive aggravated myatrophy in the proximal extremity muscles. All 28 patients in the SAR group had different levels of elevated blood CK (366 to 8,270 IU/L) and exhibited myogenic injury in the electromyograms. All patients were further confirmed through skeletal muscle biopsy and immunohistochemical staining. The 13 patients in the CON group were collected from the Department of Neuromuscular Diseases and clinically newly diagnosed with myopathy while excluding patients with sarcoglycanopathy, Duchenne, or Becker muscular dystrophy through skeletal muscle biopsy, immunohistochemical staining, and pathological analysis. Heart colour Doppler ultrasound and electrocardiogram examination revealed no abnormality in the heart. This study was conducted in accordance with the Declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Hebei Medical University. Written informed consent was obtained from all participants.

Imaging data collection

Each studied subject was intravenously injected with 111-740MBq $^{99}Tc^{m}$-MIBI ($^{99}Tc^{m}$, HTA Co., Ltd; MIBI, Beijing Shihong Pharmaceutical Centre) (radiochemical purity > 95%) in fasting and resting conditions. The dosing method was as follows: dosage = body weight (kg) / 70 × adult dose [11]. Thirty minutes later, 150–200 ml of milk was administered, and gated myocardial perfusion imaging was performed 1.5h later. The imaging apparatus used here was the Infinia VC Hawkeye dual-head single-photon emission-computed tomography (SPECT, GE, USA), together with a low-energy, high-resolution collimator. The acquisition conditions and methods were referred to the reference [11]. The electrocardiographic R-wave was used to trigger the gated synchronous acquisition (8 frames per cycle with the matrix as 64 × 64). Image analysis and processing were performed using the Xeleris functional imaging processing station (GE, USA); the image reconstruction used the filtered back projection method with Butterworth as the filter function and the system-recommended cutoff frequency and steepness factor. Images of the short, vertical long and horizontal long axis were shown after reconstruction. Quantitative gated SPECT (QGS) software was used to analyse the left ventricular ejection fraction (LVEF), end-diastolic volume (EDV), and end-systolic volume (ESV).

Image processing and result analysis

The left ventricle is divided into seven segments (the cardiac apex, anterior, anterolateral, inferolateral, inferior, inferior septum, and anterior septum wall) and 17 subsegments, including the cardiac apical, the proximal cardiac apical (anterior, septum, inferior, and lateral wall), the proximal basement (anterior, anterior interarticular, inferior interarticular, inferior, inferolateral, and anterolateral wall), and the basement (anterior, anterior interarticular, inferior interarticular, inferior, inferolateral, and anterolateral wall) subsegments. In addition, the radioactivity of each segment was scored using one 5-point scoring method (i.e. from 0 to 4 points) as follows: 0 point = normal radioactivity distribution, 1 point = mild decreased uptake, 2 points = moderate decreased uptake, 3 points = severe decreased uptake, 4 points = no radioactive uptake. According to the number of lesion-involved segments, mild lesions were limited to one segment, moderate lesions involved two segments, and severe lesions involved three segments. All the images were determined by two or more experienced nuclear medicine practitioners.

Results

Pathological analysis of skeletal muscle biopsy

Histochemical staining: All the 28 patients showed pathological changes of muscular dystrophy, together with different sizes of muscular fibre, different degrees of muscular fibre necrosis and regeneration, scattered opaque muscle fibres, hyperplasia, degeneration necrosis of connective tissue, myofibre regeneration, and obvious connective tissue hyperplasia (Fig. 1).

The immunohistochemical staining of the skeletal muscle biopsies of the SAR group of 28 patients showed attenuation/defects in the expression of α-, b-, g-, and d-sarcoglycan proteins on the myofibril membranes (by immunohistochemical staining of anti-α-, b-, g-, and d-sarcoglycan monoclonal antibodies), as shown in Figure 2.

G-MPI

The results of $^{99}Tc^{m}$-MIBI G-MPI in the CON group showed that the thickness of the myocardium of the left ventricle was uniform, and the radioactivity of each segment was evenly

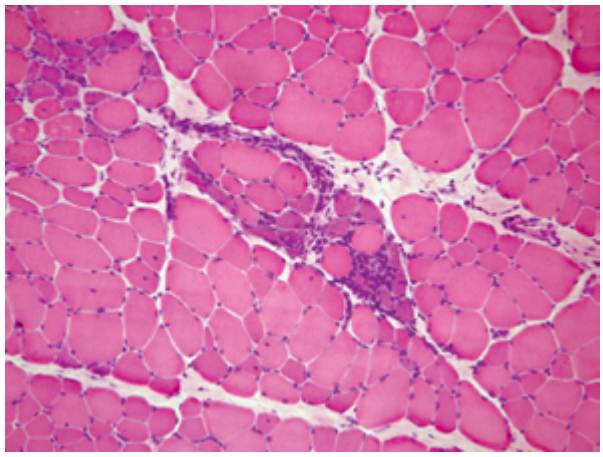

Figure 1. Pathological changes of skeletal muscle biopsy: varying muscle fibre sizes, varying degrees of muscle fibre necrosis/regeneration, scattered opaque muscle fibres, proliferation, degeneration, and necrosis of connective tissue, or myofibre regeneration (HE staining × 100)

distributed and had no sparse or defective area. The overall function of the left ventricle was normal.

Among the 28 patients in the SAR group, the results of $^{99}Tc^{m}$-MIBI G-MPI were positive in 23 patients, and the positive rate was 82.1% (23/28). Two hundred and twenty-nine subsegments with abnormal lesions were detected from the 391 subsegments of these 23 patients. According to the distribution of intra-myocardial radioactivity, the radionuclide distribution slightly decreased in 88 subsegments (1 point, 38.4%), moderately decreased in 73 subsegments (2 points, 31.9%), severely decreased in 50 subsegments (3 points, 21.8%), and no radioactivity distribution in 18 subsegments (4 points, 7.9%). According to the number of involved sites, among the 229 diseased subsegments, 41 subsegments were located at the apex, 39 subsegments were located at the anterior wall, 32 subsegments were located at the anterolateral wall, 28 subsegments were located at the inferolateral wall, 31 subsegments were located at the inferior wall, 33 subsegments were located at the inferior interarticular wall, and 25 subsegments were located at the anterior interarticular wall. Six cases exhibited abnormality in two wall segments (mild, 8.7%), two cases exhibited abnormality in three or more wall segments (medium, 26.1%), and 15 cases showed scattered lesion distribution (severe, 65.2%) (the typical cases are shown in Figure 3).

Left ventricular functional parameters

In the CON group, LVEF was 56.3 ± 3.2%, EDV was 96.7 ± 7.2 ml, and ESV was 40.4 ± 6.4 ml. Among the 23 patients that exhibited positive results with myocardial perfusion imaging, seven patients showed elevated left ventricular EDV and ESV (EDV 132.3 ± 11.7 ml, ESV 74.6 ± 9.6 ml), and four patients showed decreased LVEF 42.8 ± 2.3% with poor coordination of diffuse movement of the left ventricular wall (Fig. 4 for typical cases). The five patients with negative results of myocardial perfusion imaging showed normal LVEF, EDV, and ESV.

Discussion

Sarcoglycanopathy is a hereditary skeletal muscle disease with progressive aggravated amyosthenia and myatrophy as the main clinical manifestations, which gradually aggravates with the prolongation of the disease course. Amyosthenia and

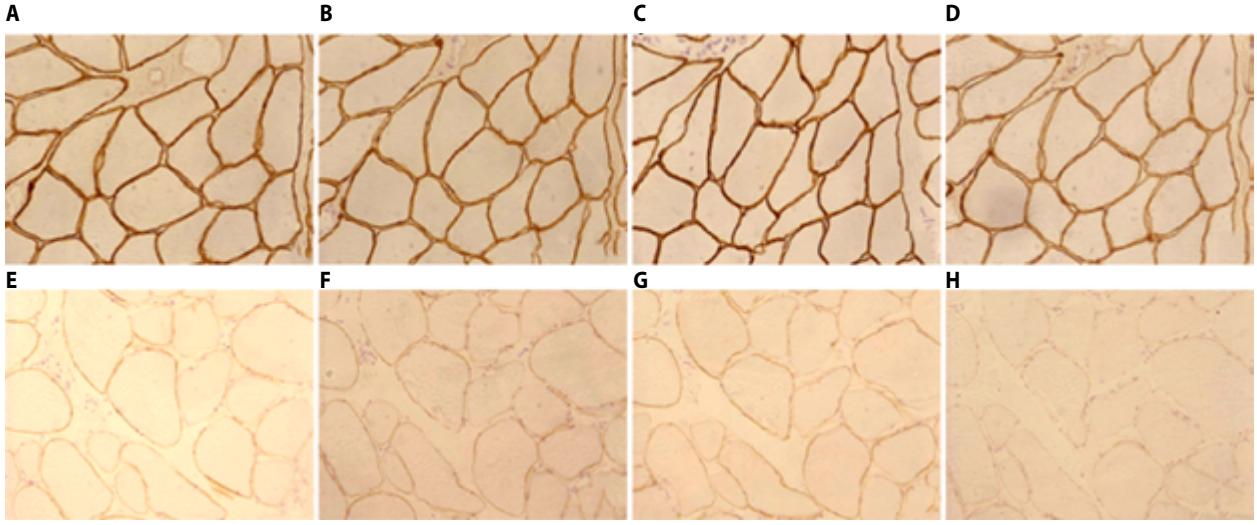

Figure 2. Pathological analysis of immunohistochemical staining. **A–D:** Patients in the CON group (patients with LGMD2B): immunohistochemical staining of anti-α-, b-, g-, and d- monoclonal antibodies shows the subunit proteins of sarcoglycan are expressed normally (× 500); **E–H:** patients in the SAR group (patients with LGMD2F): immunohistochemical staining of anti-α-, b-, g-, and d- monoclonal antibodies shows the subunit proteins of d-sarcoglycan is obviously reduced, and other subunit proteins are downregulated (× 500)

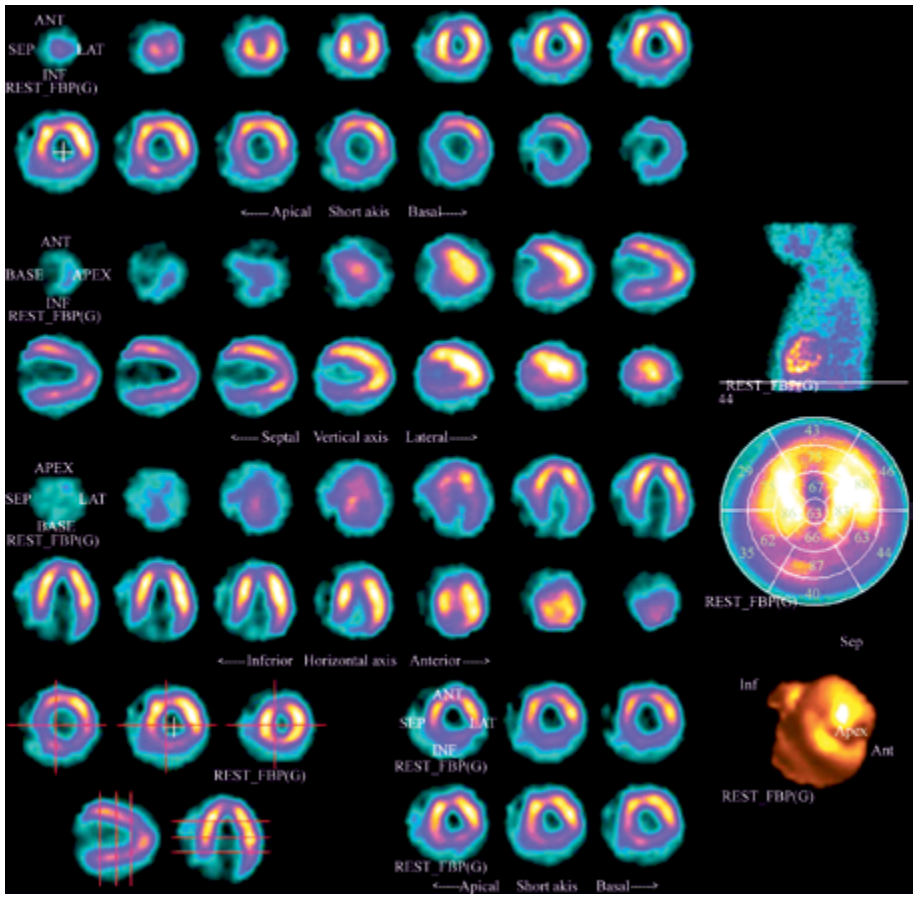

Figure 3. Gated myocardial perfusion tomography reveals that the thickness of left ventricle myocardium is not uniform, and the radioactivity distributes sparsely in the cardiac apex, anterior wall close to the apex segment, mid-anterior wall, inferior interarticular wall, and inferolateral wall

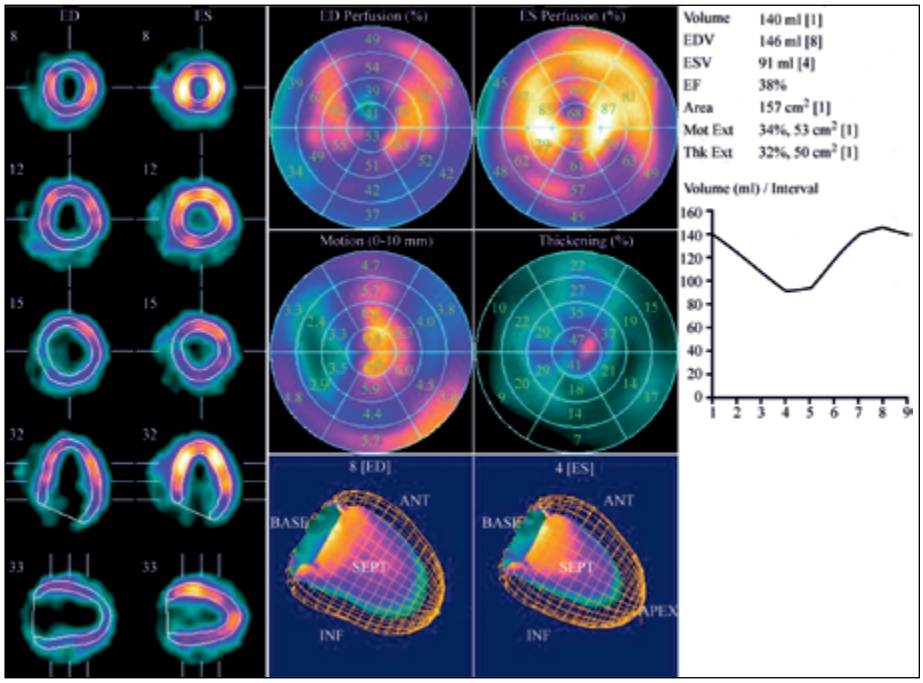

Figure 4. Gated myocardial perfusion tomography reveals EDV = 146 ml

myatrophy usually become apparent in the first or second decades. Progressive aggravated amyosthenia makes actions become more difficult, together with gradually developed and aggravated myocardial damage as the disease progresses. This will seriously affect the quality of life of the patient and place heavy economic and social burdens upon individuals, families, and society. Therefore, early detection, necessary interventions, and dynamic observation of the prognosis of myocardial lesions are crucial [12–14].

At present, there are a few studies on cardiac diseases caused by sarcoglycanopathy [15], which are mostly detected using electrocardiograms and colour ultrasound. Studies have reported that the myocardium can be affected by sarcoglycanopathy, and sometimes appears as dilated cardiomyopathy in echocardiography [15]. Studies using $^{99}Tc^{m}$-MIBI G-MPI in evaluating myocardiac damage in patients with sarcoglycanopathy are rare. In this study, $^{99}Tc^{m}$-MIBI G-MPI was performed on patients clinically diagnosed with sarcoglycanopathy, aiming to explore preliminarily the diagnostic value of this technique on myocardial lesions in patients with sarcoglycanopathy.

Of the 28 patients enrolled in this study, 23 patients exhibited positive results. The histological features of the myocardium are similar to those of skeletal muscles, as both are striated muscles and contain sarcolemmal proteins. In the case of sarcoglycanopathy, α-, b-, g-, and d-sarcoglycan form a sarcoglycan complex in the dystrophin glycoprotein complex, which is important in stabilising the cytoskeleton of the muscle and has the function of maintaining the cell membrane stability. The loss of any of these functions can result in the attenuation and disappearance of the complex protein on the cell membrane. The defect of one component of the complex causes the obstruction of the synthesis and assembly process of other proteins on the sarcolemmal membrane, which may impair the integrity and stability of the sarcolemma structure, followed by the degeneration and necrosis of muscular cells [16]. The myocardial uptake of $^{99}Tc^{m}$-MIBI is closely related to the integrity of the myocardial cell membrane [17], which in turn affects the uptake of $^{99}Tc^{m}$-MIBI by the cardiac myocytes, resulting in abnormal changes such as sparseness. The defect in the complex protein may be an important pathogenic factor for sarcoglycanopathy combined with cardiomyopathy.

The degeneration and necrosis of cardiomyocytes in patients with sarcoglycanopathy occur and disperse in multiple sites. The characteristic of its myocardial perfusion imaging appears to be scattered multiple focal lesions (mostly multilaminar myocardial involvement), patchy myocardium, and non-segmental (having nothing to do with the shape of the coronary artery, and different from coronary artery stenosis-resulted myocardial ischaemia in the coronary artery--dominating area). $^{99}Tc^{m}$-MIBI imaging can objectively reflect whether the myocardial cell function is normal [17]. Therefore, this study can objectively reflect myocardial ischaemia caused by paediatric coronary artery disease. The changes in cardiac function found in this study focused on patients with multi--wall lesions; the severity of myocardial damage as well as the state of cardiac function may be related to the extent and the course of such pathological changes as in myofibre necrosis and connective tissue hyperplasia.

Among the 28 patients, five exhibited negative results with $^{99}Tc^{m}$-MIBI G-MPI. The explanation may be that recent studies have found that sarcoglycan has other subunits, namely ε and ζ-sarcoglycan. These two subunits are mainly found in the smooth muscle but distribute only in small amounts in the skeletal muscle [18]. The defective subunit protein of sarcoglycanopathy determines the degree of involvement of myocardial lesions. If the defective subunit protein is predominantly distributed in the skeletal muscle but in a small amount in the myocardium, an obvious defect of this subunit protein may be found in the skeletal muscle by immunohistochemical staining while myocardial damage may be milder. This may be determined by the subunit protein. With the differences in the subunit proteins, the clinical phenotypes may be different. Politano et al. [19] performed electrocardiography, echocardiography, and pulmonary function assessments on 20 patients with sarcoglycanopathy and found that 31.3% of the patients had normal cardiac function, 43.7% had subclinical myocardium disease, 6.3% of patients had arrhythmia myocardium disease, and 18.7% showed dilated cardiomyopathy. Hypoxic myocardial damage occurring at β, γ, and δ, and γ and δ normally shows changes in the dilated cardiomyopathy. Fayssoil et al. [20] compared the cardiac function data of eight patients with α-type sarcoglycanopathy and that of 11 patients with γ-type sarcoglycanopathy using echocardiography, and found that the cardiac function in patients with γ-type sarcoglycanopathy is more vulnerable compared to that of patients with α-type sarcoglycanopathy (LVEF: 45.6 ± 1.8% vs. 59.6 ± 5.9%, P = 0.018). In addition, it may be related to the course of the disease to certain extent.

In this study, the positive rate of $^{99}Tc^{m}$-MIBI G-MPI was 82.1%. This inspection method is safe, non-invasive, and repeatable. The limitations of this study are that the results were affected by the types of disease, and the number of cases was limited. Our future studies will gradually increase the case number. Some hereditary and metabolic skeletal muscle diseases involve the myocardium and are relatively invisible in the early stages. Late-stage revealing is one of the most important causes of death in such patients. When the pathological changes of the skeletal muscle are involved, myocardial involvement should not be spared. $^{99}Tc^{m}$-MIBI gated myocardial perfusion tomography can dynamically show myocardial lesions, thus providing as early diagnosis and intervention as possible so as to improve the survival of such patients. The $^{99}Tc^{m}$-MIBI myocardial rest imaging can visually show the location, extent, and degree of the diseased myocardium, thus providing great help for the judgment of clinical condition. Therefore, as a routine, simple, non-invasive, and high-diagnostic method, it has a high value, which can be used not only for early diagnosis of myocardial injury, but also for long-term follow-up studies.

Acknowledgements: *This work was supported by the Research Project of Excellent Talents in Clinical Medicine funded by Hebei Provincial Government.*

Conflicts of interest: *The authors declare no conflict of interest.*

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RESEARCH PAPER

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2019, Volume 53, no. 4, pages: 271–276
DOI: 10.5603/PJNNS.a2019.0033

ISSN 0028–3843

Multiple sclerosis: oral health, behaviours and limitations of daily oral hygiene — a questionnaire study

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ABSTRACT

Clinical rationale for the study. Neurological deficits and progressing disability in patients with multiple sclerosis (MS) may hamper daily oral hygiene, but their relations with oral problems have not yet been clearly determined.

Aim of the study. The aim of this study was to identify the most significant dental problems and limitations of daily oral hygiene in Polish patients with MS.

Material and methods. 199 patients with diagnosed MS (median age 37 years) treated in the neurological outpatient clinic were interviewed using a paper-based questionnaire. They provided answers on oral health, behaviours and the limitations of their daily oral hygiene. Clinical information regarding symptoms, MS phenotype, relapses, medication and degrees of disability was based on medical records.

Results. The most frequent symptoms were dry mouth (43.2%) and bleeding from gums (28.1%). Dry mouth was more frequent in patients with secondary-progressive MS (SPMS) than relapsing-remitting MS (65.4% *vs* 41.3%, p = 0.023). Patients with bleeding from gums had had MS for a longer duration (median 6 *vs* 4 years, p = 0.002). Difficulties in daily oral hygiene were more frequent in patients with SPMS (24.0% *vs* 8.1%; p = 0.016). Greater proportions of patients with muscle weakness of limbs, imbalance or pain brushed their teeth irregularly. Frequent (i.e. at least every six months) visits to the dentist's surgery were uncommon in patients with SPMS (12.0% *vs* 39.7%, p = 0.010).

Conclusions and clinical implications. Dry mouth and bleeding from gums are more frequent in patients with longer lasting and more advanced types of MS. Daily oral hygiene and oral health self-control is limited in patients with MS, mainly due to motor deficits, balance problems and pain, and this becomes worse with disease duration.

To minimise the burden of the disease, patients with MS require better education and improvement in their awareness regarding proper oral health control, such as the use of electric toothbrushes. In addition, patients with chronic and progressive disability from multiple sclerosis may benefit from better organised access to dental care.

Key words: multiple sclerosis, oral health, oral hygiene, questionnaire

(Neurol Neurochir Pol 2019; 53 (4): 271–276)

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Introduction

Multiple sclerosis (MS) is a chronic, inflammatory, demyelinating and neurodegenerative disease of the central nervous system (CNS), which damages myelin sheaths, oligodendrocytes, as well as nerve cells and axons. It is characterised by gradual and progressive limitation of functional abilities, consequently leading to disability. The first symptoms of the disease usually appear between the ages of 20 and 40 years, and therefore MS is considered the most common cause of disability in younger people [1].

Individual clinical presentations, and the rate of accumulation of disability, may be different in each patient and depend on the location and the amount of demyelinating lesions in the CNS. Clinical symptoms of MS include, but are not limited to, motor deficits, sensory disturbances, visual disorders, bulbar symptoms, cognitive dysfunction, dysautonomia and mental disorders [2–8], which individually or in combinations may hamper oral hygiene. Progressive functional disability and medication used for the treatment of MS may also be associated with greater incidences of oral diseases and dental problems [9–13].

Daily oral hygiene, frequency of visits to the dentist's surgery, and mouth discomfort have been identified as the main dental problems requiring medical attention in patients with MS [9–15]. To date, there has been no study of oral problems or difficulties in oral hygiene in patients with MS in Poland. Therefore, the purpose of this study was to identify the most significant limitations of daily oral hygiene in Polish patients with MS, to assess the incidence and type of dental problems, and to evaluate their association with clinical features, as well as social and economic factors.

Material and methods

Consecutive subjects were recruited among patients with MS diagnosed according to the 2010 McDonald criteria [16], who were treated in the Neurological Outpatient Clinic at the Department of Neurology of Medical University of Silesia (Zabrze) between 1 July 2014 and 31 January 2015. The study was conducted according to the principles of the Declaration of Helsinki and all participants provided written informed consent. The protocol of the study was reviewed and approved by Ethics Committee of our institution.

Each patient was interviewed using a questionnaire devised by ourselves, and provided answers to several general and specific questions. General questions concerned age, sex, education, professional activity, familial status, course of the disease (age of first symptoms and diagnosis, phenotype of MS, current symptoms, number and frequency of relapses during the disease course, previous and current medication) and comorbidities. Clinical information about relapses, medication and disability degree measured with Expanded Disability Status Scale (EDSS) [17] was verified with the outpatient's neurological documentation. Specific questions concerning dental health status and dental care included: frequency of visits to the dentist's surgery, time since the last visit, behaviours and habits of oral hygiene, problems with daily oral hygiene, oral sensations, preferences for specific foods or drinks, and history of smoking.

Statistical analysis was performed using STATISTICA 12 software (Stat Soft, Poland) and R 3.3.2 (GNU General Public License). Data were presented as means with standard deviation (± SD), median with minimum and maximum values or as percentages. After checking for normality with the Shapiro-Wilk test, to analyse the between-groups differences Student's t-test or Mann-Whitney *U* test were used and chi-square or Fisher's exact tests were used for categorical data. A p value < 0.05 was considered significant.

Results

The study included 199 patients (143 women; 71.9%) with diagnosed MS (median age 37 years, range 18–67 years) and with a median duration of 4 years (range 0–27 years) since diagnosis. Socioeconomic and clinical data of the studied group are given in Table 1. In general, patients with secondary progressive MS (SPMS) were older than those with the relapsing-remitting form of MS (RRMS) (median age 48.5 years, 29–67 years *vs* 36 years, 18–65 years, respectively; $p < 0.001$) and on average had had the disease for longer (median 6 years from diagnosis, 1–24 years, *vs* 4 years, 1–27 years, respectively), but this difference was not statistically significant ($p = 0.076$).

Oral and dental problems

Dry mouth and bleeding from gums were the most frequent symptoms reported by 86 (43.2%) and 56 (28.1%) patients with MS, respectively. The incidence of oral and dental problems, limitations and behaviours of oral hygiene is summarised in Table 2. The most frequent symptoms (dry mouth and bleeding from gums) were not related to the age of the patient ($p = 0.392$ and $p = 0.877$, respectively). However, the incidence of dry mouth was higher in patients with SPMS than in patients with RRMS (65.4% *vs* 41.3%, respectively; $p = 0.023$). The incidence of bleeding from gums was not different between patients with SPMS or RRMS ($p = 0.873$), but patients with bleeding from gums had had their disease for longer than patients without (median 6 years, 0–27 years, *vs* 4 years, 0–24 years, respectively; $p = 0.002$).

There was no difference in the incidence of dry mouth and bleeding from gums between patients using Disease Modifying Drugs (DMD) or not ($p = 0.994$ and $p = 0.662$, respectively), nor they were associated with the use of any specific DMD ($p = 0.230$ and $p = 0.363$, respectively). Dry mouth was more frequent in patients who reported that they had received at least one course of steroids in the past (50.0% *vs* 31.3%; $p = 0.013$). On the other hand, it was not associated with any type of symptomatic treatment for MS, in which dry mouth may

Table 1. Socioeconomic and clinical data of 199 patients with multiple sclerosis (MS)

	Patients; n (%)
Education	
Elementary	4 (2.0)
Secondary	68 (34.2)
High	90 (45.2)
Undergraduate	36 (18.1)
Professionally active	116 (58.3)
Number of children	
0	77 (38.7)
1	58 (29.2)
2	56 (28.1)
≥3	8 (4.0)
Marital status	
Single	75 (37.7)
Married or in partnership	124 (62.3)
Economic status (income)	
Above high	14 (7.0)
High	93 (46.3)
Average	89 (44.7)
Low	2 (1.0)
Phenotype of MS	
Relapsing-remitting MS	151 (75.9)
Secondary progressive MS	26 (13.1)
No data	22 (11.0)
EDSS score (mean ± SD)	3.2 ± 1.9
Number of relapses per year (mean ± SD)	1.3 ± 0.9
Time from last relapse; months (mean ± SD)	21.5 ± 23.7
Reported symptoms of MS	
Muscle weakness in at least one limb	143 (71.9)
Sensory disturbances	134 (67.3)
Balance problems	111 (55.8)
Pain (different localisations)	54 (27.0)
Visual disturbances	13 (6.5)
Fatigue	4 (2.0)
Disease Modifying Drugs (DMD) received	
Interferon beta	112 (56.3)
Glatiramer acetate	19 (9.5)
Fingolimod	19 (9.5)
Natalizumab	4 (2.0)
No DMD	37 (18.7)
No data	8 (4.0)
Methylprednisolone (at least once in a lifetime)	92 (46.2)
Main symptomatic MS treatment (indication)	
Myorelaxants (spasticity)	9 (4.5)
Antiepileptic drugs (sensory disturbances)	8 (4.0)
Amantadine (fatigue)	4 (2.0)
Oxybutynin (urine urgency)	3 (1.5)
Comorbidities	
Thyroid disease	27 (13.7)
Arterial hypertension	25 (12.6)
Coronary artery disease	5 (2.5)
Chronic urinary tract infection	4 (2.0)
Mental disorders	4 (2.0)
Liver diseases	4 (2.0)
Diabetes mellitus	2 (1.0)
Oral contraceptives (women only)	4 (2.8)
Active cigarette smokers	55 (28)
Alcohol consumption	
Regular	124 (62.3)
At least once a week	8 (4%)

Note: Unless otherwise indicated, presented data are numbers of patients in the studied group (with respective percentages given in brackets). SD – standard deviation; EDSS – Expanded Disability Status Scale

be one of the side effects (mainly myorelaxants, antiepileptic drugs, amantadine, oxybutynin, oral contraceptives or antidepressants) (p = 0.127). Bleeding from gums was not associated with steroid use or any concomitant medication (p = 0.660).

Daily oral hygiene

Difficulties with daily oral hygiene were reported more often by patients with SPMS than by patients with RRMS (24.0% *vs* 8.1%; p = 0.016). Patients with selected neurological focal deficits related to MS also more frequently reported difficulties with daily oral hygiene than did patients without them: 1) muscle weakness of limbs (23.4% *vs* 5.8%, respectively; p < 0.001); 2) imbalance (27.3% *vs* 6.8%, respectively; p < 0.001); and 3) pain (25.0% *vs* 8.9%, respectively; p = 0.030). Additionally, insufficient brushing of the teeth – once a day or less – was significantly more frequent in patients with muscle weakness of limbs, imbalance or pain, than in those without these specific symptoms – two or three times per day (29.8% *vs* 15.0%, p = 0.007; 33.3% *vs* 15.0%, p = 0.029 and 35.0% *vs* 16.4%, p = 0.046, respectively). Patients with bleeding from gums less often used an electric toothbrush (8.9% *vs* 22.5%; p = 0.028) and brushed their teeth less frequently, but this difference was not significant (p = 0.067). Reported problems with oral hygiene were not associated with gender, age, education,

Table 2. Oral problems, behaviours and limitations of oral hygiene reported by 199 patients with multiple sclerosis (MS). Data presented as n (%)

	Patients; n (%)
Oral and dental problems	
Dry mouth	86 (43.2)
Bleeding from gums	56 (28.1)
Metallic flavour in the mouth	21 (10.6)
Dysgeusia	20 (10.1)
Pain during brushing the teeth	10 (5.0)
Burning in the mouth	8 (4.0)
Difficulties in daily oral hygiene	
Minor	17 (8.5)
Moderate	4 (2.0)
Help from another person	1 (0.5)
No data	4 (2.0)
Brushing of teeth	
Three or more times a day	34 (17.1)
Twice a day	123 (61.8)
Once a day	36 (18.1)
Occasionally	2 (1.0)
No data	4 (2.0)
Toothbrush used	
Traditional	159 (79.9)
Electric	36 (18.1)
No data	4 (2.0)
Additional behaviours of oral hygiene	
Mouth fluid	84 (42.2)
Dental floss	79 (39.7)
Irrigator	3 (1.5)
Visits to the dentist's office	
Every six months	69 (34.7)
Once a year	68 (34.2)
Less than once a year	30 (15.1)
Only in an emergency	26 (13.1)
No data	6 (3.0)
Last visit to the dentist	
Less than six months ago	49 (24.6)
Between six and 12 months ago	79 (39.7)
More than 12 months ago	39 (19.6)
No data	32 (16.1)
Fear of dentists	56 (28.1)
Nutritional preferences (regular consumption)	
Sparkling water	137 (68.8)
Meat	134 (67.3)
Vitamin supplements	120 (60.3)
Fruit juices	90 (45.2)
Flour products	81 (40.7)
Sweet drinks	29 (40.6)
Sweets	76 (38.2)
Sweets in the evening after teeth brushing	52 (26.1)
Still water	48 (24.1)

professional activity, marital, familial and economic status, degree of disability (EDSS), comorbidities, used MS therapy or mean number of relapses per year.

Oral health self-control

Regular (at least every six months) visits to the dentist's surgery were reported by a greater proportion of patients with RRMS than those with SPMS (39.7% *vs* 12.0%), and therefore a greater proportion of patients with SPMS visited the dentist less frequently than patients with RRMS (52.0% *vs* 33.6% at least once a year and 28.0% *vs* 11.6% less than once a year, respectively; $p = 0.010$). Women and patients with a better level of education visited the dentist's more often than others ($p = 0.010$ and $p = 0.001$, respectively). The frequency of visits was not associated with age, professional activity, marital, familial and social status, degree of disability, reported symptoms, concomitant diseases, type of therapy used or the annual number of relapses.

Discussion

In the presented study, the main reasons for oral discomfort in Polish patients with MS were xerostomia (43.2%) and gingival bleeding (28.1%). The prevalence of xerostomia in the general population ranges significantly, from 0.9% to 64.8% [18], depending on the population studied and the methodology used. In our study, the frequency of xerostomia in patents with MS was considered high, because our patients were on average younger than the overall general population, and problems with a dry mouth are usually more prevalent among the elderly [19].

Dry mouth was more frequent in patients with the secondary progressive MS phenotype and those who had used steroids in the past. In our opinion, this is less likely to be a specific side effect of steroids use and more likely to be part of this type of MS, because patients with SPMS are older, have had their disease for longer, have more neurological symptoms, and there is a higher chance that they were treated with steroids in the past [20]. It is possible that dysautonomia and sensory disturbances in long-lasting MS may be the cause of xerostomia in these patients, but such a hypothesis requires further investigation. On the other hand, steroids are recommended in the treatment of Sjögren's syndrome, an autoimmune disease in which the main symptoms are dry eyes and mouth, so a short course of steroids (even repeated) can be beneficial for xerostomia [21].

Dry mouth was not associated with the use of DMD, nor with any specific medication. This is consistent with the general risk profile of most newer-generation DMDs – e.g. interferons, glatiramer acetate, fingolimod or natalizumab – compounds that were used in our patients. Against this, teriflunomide has been reported to raise the risk of tooth loss [22], but none of our patients was receiving this treatment. Medication used in the symptomatic management of MS may have the potential to cause dry mouth and other oral diseases [9, 13]. Individual patients in our group were taking baclofen, amantadine,

oxybutynin or contraceptive drugs, but the overall incidence of xerostomia was not higher, probably because of the significant heterogeneity of the group and only single patients receiving such treatment. Tobacco use is often the cause of dry mouth [23], but in the studied group the proportion of active cigarette smokers was comparable to that in the general population.

Bleeding from gums was reported by less than 28.1% of patients with MS, compared to a 50% incidence of gingival bleeding in healthy Poles [24]. The average age of responders in that study was higher, by more than a dozen years, than in our group and gingival bleeding was largely related to the fact of brushing the teeth and the type of toothbrush bristles (soft, medium, hard). In our group, patients with bleeding from gums significantly less often brushed their teeth using an electric toothbrush (2.5 times less frequently), therefore a manual toothbrush could be the one of the risk factors for gingival bleeding. In other populations of patients with MS, this incidence of gingival bleeding has been estimated as being 5–15% [12, 25]. This difference could be the result of a different methodology of acquisition of data, as we questioned patients about any possible incident of gingival bleeding, whereas in other studies this symptom could be actually confirmed during an intraoral examination.

Substantial difficulties and limitations of daily oral hygiene were reported by about 11% of patients with MS, and they were three times more frequent in patients with SPMS than in RRMS (24% *vs* 8%). Patients with SPMS may have more severe neurological deficits and higher degrees of disability to interfere with oral hygiene and access to dental services [20]. We identified weakness of limbs, imbalance and pain to be the main factors limiting daily oral hygiene. In other studies in patients with MS, visual disturbances, facial pain, trigeminal neuralgia, paresthesia, spasticity, spasms, tremor, fatigue and depression have also been found [9, 13], but our group consisted of younger participants and with a shorter disease duration than the general population of patients with MS, therefore with less disease-related burden.

Oral hygiene in patients with MS rarely attracts the attention of neurologists, but dental problems should be expected and explored, particularly because of the chronic character of the disease and the progressive disability of patients. In our study, 61.8% of patients with MS said that they brushed their teeth twice a day, which is a higher proportion than estimated in the general Polish population (54.7%) [26]. A similar proportion was observed in a British population of patients with MS (66%), although this was less often than in the general population in the UK (74%) [27]. Individual neurological deficits reported by studied patients, mainly weakness of limbs, imbalance and pain, were significant factors contributing to irregular (once a day or less) brushing of the teeth.

Additional aids can help in maintaining proper oral health in individuals with significant neurological deficits. Unfortunately, in the studied group a hygiene fluid was used less frequently (42.2%) than in healthy Poles (67%), as was dental floss (39.7% *vs* 57%) [26]. Electric brushes can reduce plaque by 7–57.9%, gingival inflammation by 17–19.8%, and bleeding of gingiva by 85.2%, and they are more effective compared to manual brushes [28]. In our study, almost 80% of patients with MS used manual toothbrushes (in this group was more gingival bleeding), which is 13% more than in the general Polish population. Neurologists should educate patients about proper oral hygiene, because immunosuppressive therapy or corticosteroids may additionally raise the risk of oral infections in patients with MS [29].

Active participation of individuals in dental health self-control was significantly limited in our patients with MS. Only 24.6% of patients reported that they had visited the dentist within the last six months, compared to 56% of adult healthy Poles [26]. Patients with SPMS visited dentists significantly less frequently than patients with RRMS, therefore functional disability could be one of the reasons for worse oral health self-care. However, we suspect that not only neurological deficits were responsible, because in the comparable group in the UK, 81% of MS patients and 71% of non-MS subjects claimed to visit the dentist at least once a year [27], which was reported only by 34.2% patients from the studied group. This means that dental care in Poland is less available, probably because of architectonical barriers, insufficient awareness of healthy behaviours or anxiety regarding the dentist. This finding was surprising, because patients with MS in our study were younger than the overall population with MS and so would be expected to be more proactive in such behaviours.

The advantage of the presented study is the quite large studied group and clinical data verification with clinical neurological documentation. However, limitations to the study are one-time observation and the collection of data only by questionnaire and without a dentist's visual evaluation. Enrolled patients were younger than the general population, younger than the general population of patients with MS, and with a shorter disease duration. We see this study as a preliminary report. Research will be continued, especially in older MS patients, and also in those with primary progressive MS.

Conclusions and clinical implications

Patients with MS may complain about similar conditions causing oral discomfort as healthy individuals, such as dry mouth and bleeding from gums, but these symptoms are more frequent and more pronounced in patients with longer lasting and more advanced types of the disease. Daily oral hygiene, as well as regular oral health self-control, is substantially limited in patients with MS, mainly due to motor deficits, balance problems and pain, and this becomes worse with disease duration. To minimise the burden of the disease, patients with MS require better education and improved awareness about proper oral health control, such as the use of electric toothbrushes. In addition, patients with chronic and progressive disability from multiple sclerosis may benefit from better organised access to dental care.

Financial support: *None declared.*

Conflict *of interest*

KKB, EK, KP received travel support and/or compensation for lectures and/or participation in advisory boards from Biogen, Genzyme, Merck Serono, Novartis, Roche, and Teva, which have been exclusively used for the support of research activities. BLR received travel support and/or compensation for lectures and/or participation in advisory boards from Teva, which have been exclusively used for the support of research activities. MA is an employee of Novartis. The other authors declared no conflict of interest.

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RESEARCH PAPER

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2019, Volume 53, no. 4, pages: 277–290
DOI: 10.5603/PJNNS.a2019.0034

ISSN 0028–3843

Epidemiological analysis of hospitalisations due to recurrent stroke in the Silesian Province, Poland, between 2009 and 2015

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ABSTRACT

Background and aim. There is a lack of recent epidemiological studies on recurrent stroke (RS) in Poland. The aim of this study was to analyse all hospitalisations related to RS in Silesia – an industrial region covering 12% of the Polish population.

Material and methods. We carried out statistical analysis of data contained in stroke questionnaires transferred to the Polish National Health Fund by hospitals in Silesia, Poland, between 2009 and 2015.

Results. In the analysed period, the number of RS hospitalisations in Silesia was 18,063 (22.2% of all acute strokes). The percentage of RS significantly decreased during the period under consideration ($p < 0.001$). The same observation concerned recurrent ischaemic stroke (RIS), but not recurrent haemorrhagic stroke (RHS). The median hospitalisation time was 14 days for RHS, and 11 days for RIS. Large-artery atherosclerosis and cardioembolisms were significantly more often recognised in RIS than in first-ever ischaemic stroke (FIS) (consecutively, 38.2% *vs* 36.0%, and 21% *vs* 18.1%; $p < 0.001$). The in-hospital mortality rate was significantly higher for RS than for first-ever stroke (18.4% *vs* 17.2%; $p < 0.001$). The same observation was done for RIS vs FIS (16.2% *vs* 13.9%; $p < 0.001$), and for RHS vs FHS (39.8% *vs* 36%; $p = 0.004$). The rtPA therapy was applied to 5.3% of FIS and 3.2% of RIS patients ($p < 0.001$).

Conclusions. This is the first such comprehensive and long-term analysis of recurrent stroke in Silesia, Poland. It could help in the implementation of appropriate educational programmes, and thus help to improve the health status of society.

Key words: stroke, epidemiology, ischaemic stroke, haemorrhagic stroke, recurrent stroke

(*Neurol Neurochir Pol 2019; 53 (4): 277–290*)

Introduction

Stroke constitutes the third highest cause of death and the main cause of permanent disability in adults in Europe. Due to its poor prognosis, and the high costs of treatment and of chronic care, stroke is not only a medical but also a social problem.

Recently conducted epidemiological studies have significantly improved our understanding of stroke epidemiology and treatment. But regular updates at local, national and global levels are needed. The first epidemiological data on cerebrovascular diseases in Poland comes from the years 1980–2010 [1–13]. The most recent studies, both national and regional, were conducted in the last decade [14–17]. Some

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of them have concerned the Silesian Province, an industrial region of Poland covering 12% of the nation's population (4.6 million people). In these studies, we have analysed the local incidence of first-ever-stroke (FS), the number of stroke hospitalisations, stroke aetiology, outcome, used methods of diagnostics, and treatment between 2009 and 2015 [15, 16].

However, there is still a lack of recent epidemiological data on recurrent stroke (RS) in Poland despite the fact that this is a known indicator of the effectiveness of secondary stroke prevention.

Therefore, the aim of this study was to assess the epidemiological characteristics of RS in the Silesian Province of Poland over the course of the last decade.

Materials and methods

Our study was based on data obtained from stroke questionnaires (n = 88,425) which were mandatorily reported to the National Health Fund (NHF; the only public health insurer in Poland) by all Silesian hospital departments for stroke patients (homogeneous patient groups: A48-A51). The analysed period was between 2009 and 2015. The study was carried out with the approval of the Silesian division of the NHF and the Consultant in Neurology for the Silesian Province.

The questionnaire was verified for incomplete or recurring data (e.g. recurring records of the same hospitalisation were excluded). Finally, 81,193 stroke questionnaires were enrolled for analysis. A diagnosis of stroke was made according to the International Classification of Diseases version 10 (ICD-10).

The following data from the stroke questionnaires were used in the present study: age, sex, admission date, date of the first occurrence of stroke symptoms, date of death or discharge, number of hospitalisation days, aetiology of ischaemic stroke (IS) (according to the Trial Org 10172 in Acute Stroke Treatment - TOAST), clinical symptoms (consciousness disorders, hemiparesis/hemiplegia, speech disorders, sensory disorders, posterior circle syndrome), secondary stroke prevention (antiplatelets, anticoagulants, antihypertensives), information on referral for vascular intervention due to artery stenosis, and application of recombinant tissue plasminogen activator (rtPA).

The questionnaires also included information as to whether the stroke was classified as first-ever-stroke (FS) or recurrent stroke (RS). FS was diagnosed when the response to the question "Was it your first stroke accident?" was "Yes", and RS when the response was "No".

According to the Bioethics Committee, the study was not a medical experiment. Therefore, no approval of the Committee was required.

Statistical analysis was done using SAS statistical package version 9.4 (SAS Institute Inc., Cary, NC, USA). The level of statistical significance was set at $p < 0.05$.

For nominal data, percentage values were used. The correlation between the nominal variables was verified using the $\chi 2$ test. Normally distributed quantitative data were characterised using the mean and the standard deviation, whereas the median and the interquartile range was used for non-normally distributed data. The verification of the distribution of the variables and the agreement with the normal distribution were made using the Shapiro-Wilk test. The mean difference significance was verified using the Student's t-test for two groups and the ANOVA test for three or more groups. The consistency of the distribution was verified using the Mann-Whitney U test for two groups and the Kruskal-Wallis test for three or more groups for skewed distributions. Multiple comparisons were made based on post-hoc test results for variance analysis (ANOVA) and the Kruskal-Wallis test and with the Holm-Bonferroni correction to assess significance of the percentage difference in cases of three or more groups. The test for trend was also calculated for consecutive years by means of Jonckheere-Terpstra and Cochran-Armitage tests for continuous and categorical variables, respectively.

Results

Based on analysis of the data obtained from the stroke questionnaires, the number of RS hospitalisations in the Silesian Province between 2009 and 2015 was 18,063 (9,229 women and 8,715 men; $P < 0.001$; in 119 cases sex was not recorded). In 4,763 subjects, the type of stroke (first or recurrent) could not be determined (Tab. 1).

RS constituted 22.2% of all acute stroke hospitalisations in the analysed period. The number of hospitalisations due to recurrent haemorrhagic stroke (RHS; I60, I61, I62) was 1,619 (15% of all hospitalisations with acute haemorrhagic stroke i.e. HS diagnosis), while the total number of hospitalisations due to recurrent ischaemic stroke (RIS; I63) was 16,256 (23.4% all hospitalisations with acute IS diagnosis) (Tab. 3, 4).

The percentage of RS significantly decreased during the period under consideration ($p < 0.001$). The same observation concerned RIS, but not RHS (Tab. 1, 3, 4).

The median age for patients with RS was 74 (range 66–81) years. The age of male patients (71 (range 63–78) years) was statistically significantly lower ($P < 0.001$) compared to female patients (78 (70–84) years).

The median age for patients with RIS was 75 (range 66–81) years. The age of male patients (71 (range 63–79) years) was statistically significantly lower ($P < 0.001$) compared to female patients (78 (range 70–84) years).

The median age for patients with RHS was 72 (range 62–80) years. The age of male patients (69 (range 61–77) years) was statistically significantly lower ($P < 0.001$) compared to female patients (76 (range 66–82) years) (Tab. 5).

Large-artery atherosclerosis and cardioembolisms were significantly more often recognised in RIS than in first-ever ischaemic stroke (FIS) (consecutively, 38.2% *vs* 36.0%, and 21% *vs* 18.1%; $p < 0.001$). On the other hand, lacunar stroke was less

Table 1. Number of acute (first and recurrent) stroke-related hospitalisations in the Silesian Province between 2009 and 2015 (no data on sex in 487 patients in 2012)

Year		Number of hospitalisations due to acute stroke N (%)	Number of hospitalisations in women N (%)	Number of hospitalisations in men N (%)
2009	All	11,083 (100)	5,697 (100)	5,386 (100)
	FS	7,987 (72.1)	4,061 (71.3)	3,926 (72.9)
	RS	**2,559 (23.1)**	**1,338 (23.5)**	**1,221 (22.7)**
	ND	537 (4.9)	298 (5.2)	239 (4.4)
2010	All	11,751 (100)	6,126 (100)	5,625 (100)
	FS	8,598 (73.2)	4,465 (72.9)	4,133 (73.5)
	RS	**2,681 (22.8)**	**1,391 (22.7)**	**1,290 (22.9)**
	ND	472 (4)	270 (4.4)	202 (3.6)
2011	All	11,921 (100)	6,139 (100)	5,782 (100)
	FS	8,618 (72.3)	4,409 (71.8)	4,209 (72.8)
	RS	**2,789 (23.4)**	**1,443 (23.5)**	**1,346 (23.3)**
	ND	514 (4.3)	287 (4.7)	227 (3.9)
2012	All	11,912 (100)	5,905 (100)	5,520 (100)
	FS	8,690 (72.9)	4,282 (72.5)	4,052 (73.4)
	RS	**2,725 (22.9)**	**1,350 (22.9)**	**1,256 (22.8)**
	ND	497 (4.2)	273 (4.6)	212 (3.8)
2013	All	11,926 (100)	6,202 (100)	5,724 (100)
	FS	8,605 (72.2)	4,486 (72.3)	4,119 (72.0)
	RS	**2,668 (22.4)**	**1,368 (22.1)**	**1,300 (22.7)**
	ND	653 (5.5)	348 (5.6)	305 (5.3)
2014	All	11,505 (100)	5,956 (100)	5,549 (100)
	FS	8,143 (70.8)	4,261 (71.5)	3,882 (70.0)
	RS	**2,413 (21.0)**	**1,210 (20.3)**	**1,203 (21.7)**
	ND	949 (8.3)	485 (8.1)	464 (8.4)
2015	All	11,095 (100)	5,671 (100)	5,424 (100)
	FS	7,726 (69.6)	3,924 (69.2)	3,802 (70.1)
	RS	**2,228 (20.1)**	**1,129 (19.9)**	**1,099 (20.3)**
	ND	1,141 (10.3)	618 (10.9)	523 (9.6)
All	All	81,193 (100)	39,010 (100)	41,696 (100)
	FS	58,367 (71.9)	28,123 (72.1)	29,888 (71.7)
	RS	**18,063 (22.2)**	**8,715 (22.3)**	**9,229 (22.1)**
	ND	4,763 (5.9)	2,172 (5.6)	2,579 (6.2)
P[a] for trend		< 0.001	< 0.001	0.173

All – all stroke types (I60-I64); FS – first-ever-stroke; RS – recurrent stroke; ND – no data on type of stroke; [a] – Cochran–Armitage test for trend with Holm-Bonferroni correction

often diagnosed in RIS than in FIS (8.8% *vs* 10.0%; p < 0.001). The aetiology of stroke was undetermined in 30.4% of subjects of RIS compared to 34.1% of subjects of FIS (p < 0.001) (Tab. 6). The clinical manifestation of stroke was significantly more expressed in RIS than in FIS (p < 0.001) (Tab. 7).

During the analysed period, the in-hospital mortality rate for RS was 18.4%, and it was significantly higher compared to FS (17.2%) (p < 0.001). The same observation was done for RIS vs FIS (16.2% *vs* 13.9%; p < 0.001), and for RHS vs first-ever haemorrhagic stroke (FHS) (39.8% *vs* 36%; p = 0.004). The same trend was seen in women and in men (Tab. 8–10).

The median hospitalisation time was 14 (range 5–24) days for RHS, and 11 (range 9–15) days for RIS (Tab. 11). 77.2% of patients with FS and 78.9% of patients with RS were admitted to hospital on the day when stroke symptoms appeared (p < 0.001).

The rtPA therapy was applied to 2,598 patients with FIS (5.3%) and to 525 patients with RIS (3.2%) treated in hospitals

Table 2. Rt-PA therapy in patients hospitalised due to first-ever and recurrent ischaemic stroke (I63) in the Silesian Province between 2009 and 2015

Year	Number of all hospitalisations due to FIS N	Number of all hospitalisations due to RIS N	Number of all patients treated with rt-PA[a] /percentage of treated patients to all patients with I63 diagnosis /	Number of patients with FIS treated with rt-PA /percentage of treated patients to all patients with FIS diagnosis /	Number of patients with RIS treated with rt-PA /percentage of treated patients to all patients with RIS diagnosis /	P[b] FIS *vs* RIS treated with rt-PA
2009	6,584	2,277	107 /1.2%/	88 (1.3%)	17 (0.7%)	0.025
2010	7,298	2,397	196 /1.9%/	164 (2.2%)	27 (1.1%)	0.002
2011	7,314	2,517	296 /2.9%/	242 (3.3%)	50 (2%)	0.002
2012	7,339	2,469	453 /4.4%/	366 (5%)	82 (3.3%)	0.002
2013	7,353	2,422	537 /5.2%/	439 (6%)	84 (3.5%)	< 0.001
2014	6,937	2,169	806 /8.2%/	620 (8.9%)	131 (6%)	< 0.001
2015	6,600	2,005	887 (9.3%)	679 (10.3%)	134 (6.7%)	< 0.001
P[a] for trend	-	-	< 0.001	< 0.001	< 0.001	-
All	49,425	16,256	3,282 (4.7%)	2,598 (5.3%)	525 (3.2%)	< 0.001

[a] – Cochran–Armitage test for trend with Holm-Bonferroni correction
[b] – Chi^2 test with Holm-Bonferroni correction

of the Silesian Province between 2009 and 2015 ($p < 0.001$) (Tab. 2). The percentage changed between 2009 and 2015 from 1.3% (FIS) and 0.7% (RIS) to 10.3% (FIS) and 6.7% (RIS).

The overall in-hospital mortality in patients with FIS treated with rtPA (n = 396; 15.2%) was not statistically significantly higher compared to the in-hospital mortality of patients with FIS untreated with rtPA (n = 6,489; 13.9%) (P = 0.142). Also, the overall in-hospital mortality in patients with RIS treated with rtPA (n = 87; 16.6%) was not statistically significantly higher compared to the in-hospital mortality of patients with RIS untreated with rtPA (n = 2,548; 16.2%) (P = 0.885). No difference was found between the in-hospital mortality of FIS patients and the in-hospital mortality of RIS patients treated with rtPA ($p = 0.885$). Gender did not influence the in-hospital mortality in patients treated with rtPA (Tab. 12–13).

The in-hospital mortality in patients either with RIS or FIS was significantly higher in cardiogenic stroke compared to atherogenic stroke (Tab. 14–15).

The in-hospital mortality in patients either with FIS or RIS treated with rtPA was not associated with aetiology of stroke (Tab. 16–17).

Data obtained from the stroke questionnaires allowed us to determine the secondary stroke prevention therapy; 81.7% of RIS patients and 84.3% of FIS patients ($p < 0.001$) were administered antiplatelet drugs, 26.2% of RIS subjects and 23% of FIS subjects – oral anticoagulants ($p < 0.001$), and subsequently, 84.4% and 79.9% - antihypertensive drugs ($p < 0.001$) (Tab. 18). Furthermore, 3.4% of patients with FIS and 3.1% of patients with RIS were referred for vascular intervention due to artery stenosis.

In patients with cardioembolic stroke aetiology, 37.5% of subjects with FIS and 40.6% of subjects with RIS were administered anticoagulants. The percentage of patients with RIS and cardioembolic stroke treated with anticoagulants gradually increased over the subsequent years ($p = 0.033$) while a negative trend was observed for antiplatelet drugs ($p = 0.004$) (Tab. 19).

Discussion

As we described in our previous paper, the number of hospitalisations due to stroke and the incidence of first-ever-stroke in the Silesian Province were high (from 169/100,000 in 2009 to 187/100,000 in 2015), and seemed to be more akin to Eastern rather than to Western European countries [15, 18, 19]. This suggests that primary prevention of stroke may be imperfectly implemented in our country, and that the awareness of cerebrovascular risk factors is insufficient.

On the other hand, the number of recurrent strokes is the indictor of the efficiency of secondary prevention. Our study shows that hospitalisations due to recurrent stroke constituted a little more than one fifth of all hospitalisations due to acute stroke. The recurrence is higher in IS than in HS. The selected epidemiological studies show that the risk of recurrence after a first-ever stroke reaches 4% at 1 month, 13% at 1 year, and almost 40% at 10 years [20–24]. Readmission to hospital has a negative effect on the quality of a patient's life and increases socioeconomic costs [25].

We have found that the number of RS has significantly decreased during the last decade (RS constituted 23.1% of all stroke hospitalisations in 2009 but 20.1% in 2015; $p < 0.001$). In the Warsaw Stroke Registry (conducted in 1991–1992), recurrent strokes constituted 27% of all acute stroke events observed during the study [2, 3]. In our study, a decreasing number concerned RIS, but not RHS. This is consistent with other studies [20, 26]. The decreasing number of recurrent strokes could be associated

Table 3. Number of acute (first and recurrent) ischaemic stroke–related hospitalisations in the Silesian Province between 2009 and 2015

Year		Number of hospitalisations due to acute stroke N (%)	Number of hospitalisations in women N (%)	Number of hospitalisations in men N (%)
2009	All	9,275 (100)	4,789 (100)	4,486 (100)
	FIS	6,584 (71.0)	3,346 (69.9)	3,238 (72.2)
	RIS	2,277 (24.5)	1,208 (25.2)	1,069 (23.8)
	ND	414 (4.5)	235 (4.9)	179 (4.0)
2010	All	10,058 (100)	5,284 (100)	4,774 (100)
	FIS	7,298 (72.6)	3,816 (72.2)	3,482 (72.9)
	RIS	2,397 (23.8)	1,262 (23.9)	1,135 (23.8)
	ND	363 (3.6)	206 (3.9)	157 (3.3)
2011	All	10,223 (100)	5,303 (100)	4,920 (100)
	FIS	7,314 (71.5)	3,764 (71.0)	3,550 (72.2)
	RIS	2,517 (24.6)	1,318 (24.9)	1,199 (24.4)
	ND	392 (3.8)	221 (4.2)	171 (3.5)
2012	All	10,187 (100)	5,078 (100)	4,693 (100)
	FIS	7,339 (72.0)	3,632 (71.5)	3,407 (72.6)
	RIS	2,469 (24.2)	1,232 (24.3)	1,129 (24.1)
	ND	379 (3.7)	214 (4.2)	157 (3.4)
2013	All	10,289 (100)	5,393 (100)	4,896 (100)
	FIS	7,353 (71.5)	3,853 (71.4)	3,500 (71.5)
	RIS	2,422 (23.5)	1,258 (23.3)	1,164 (23.8)
	ND	514 (5)	282 (5.2)	232 (4.7)
2014	All	9,850 (100)	5,143 (100)	4,707 (100)
	FIS	6,937 (70.4)	3,653 (71.0)	3,284 (69.8)
	RIS	2,169 (22.0)	1,104 (21.5)	1,065 (22.6)
	ND	744 (7.6)	386 (7.5)	358 (7.6)
2015	All	9,521 (100)	4,890 (100)	4,631 (100)
	FIS	6,600 (69.3)	3,368 (68.9)	3,232 (69.8)
	RIS	2,005 (21.1)	1,012 (20.7)	993 (21.4)
	ND	916 (9.6)	5,10 (10.4)	406 (8.8)
All	All	69,403 (100)	35,880 (100)	33,107 (100)
	FIS	49,425 (71.2)	25,432 (70.9)	23,693 (71.6)
	RIS	16,256 (23.4)	8,394 (23.4)	7,754 (23.4)
	ND	3,722 (5.4)	2,054 (5.7)	1,660 (5.0)
P[a] for trend		< 0.001	< 0.001	0.209

FIS – first–ever ischaemic stroke (I63); RIS – recurrent ischaemic stroke (I63); ND – no data;
[a] – Cochran–Armitage test for trend with Holm–Bonferroni correction

with a better stroke care network and improvements in secondary stroke prevention.

This is also consistent with the observation that the number of stroke survivals with atrial fibrillation on anticoagulants increased from 40% in 2009 to 44% in 2015.

As regards the aetiology of RIS, this was undetermined in less than one third of patients (for comparison, in 1991–1992 this figure was more than half) [2, 3]. Such a decrease in unknown aetiology might be the result of a greater availability of diagnostic methods (such as ultrasonography, magnetic resonance, angiography, and broader cardiologic diagnostic possibilities). It is worth emphasising that undetermined RIS was rarer than undetermined FIS (30% *vs* 34%). The most common reason for RIS was large-artery atherosclerosis. Cardioembolisms were responsible for 21% of RIS (18% in FIS).

In our study we could not establish the recurrence rates for different subtypes of ischaemic stroke because the findings were anonymous. From the literature, we can see that

Table 4. Number of acute (first and recurrent) haemorrhagic stroke–related hospitalisations in the Silesian Province between 2009 and 2015

Year		Number of hospitalisations due to acute stroke N (%)	Number of hospitalisations in women N (%)	Number of hospitalisations in men N (%)
2009	All	1,604 (100)	798 (100)	806 (100)
	FHS	1,251 (78.0)	629 (78.8)	622 (77.2)
	RHS	246 (15.3)	115 (14.4)	131 (16.3)
	ND	107 (6.7)	54 (6.8)	53 (6.6)
2010	All	1,578 (100)	783 (100)	795 (100)
	FHS	1,219 (77.3)	608 (77.7)	611 (76.9)
	RHS	255 (16.2)	113 (14.4)	142 (17.9)
	ND	104 (6.6)	62 (7.9)	42 (5.3)
2011	All	1,562 (100)	747 (100)	815 (100)
	FHS	1,211 (77.5)	583 (78.1)	628 (77.1)
	RHS	245 (15.7)	108 (14.5)	137 (16.8)
	ND	106 (6.8)	56 (7.5)	50 (6.1)
2012	All	1,596 (100)	761 (100)	771 (100)
	FHS	1,260 (79.0)	604 (79.4)	605 (78.5)
	RHS	233 (14.6)	104 (13.7)	119 (15.4)
	Na's	103 (6.5)	53 (7.0)	47 (6.1)
2013	All	1,518 (100)	740 (100)	778 (100)
	FHS	1,169 (77.0)	584 (78.9)	585 (75.2)
	RHS	220 (14.5)	97 (13.1)	123 (15.8)
	Na's	129 (8.5)	59 (8.0)	70 (9.0)
2014	All	1,531 (100)	740 (100)	791 (100)
	FHS	1,125 (73.5)	557 (75.3)	568 (71.8)
	RHS	219 (14.3)	94 (12.7)	125 (15.8)
	Na's	187 (12.2)	89 (12.0)	98 (12.4)
2015	All	1,439 (100)	711 (100)	728 (100)
	FHS	1,038 (72.1)	511 (71.9)	527 (72.4)
	RHS	201 (14.0)	105 (14.8)	96 (13.2)
	Na's	200 (13.9)	95 (13.4)	105 (14.4)
All	All	10,828 (100)	5,280 (100)	5,484 (100)
	FHS	8,273 (76.4)	4,076 (77.2)	4,146 (75.6)
	RHS	1,619 (15.0)	736 (13.9)	873 (15.9)
	Na's	936 (8.6)	468 (8.9)	465 (8.5)
P[a] for trend		0.476	0.957	0.305

FHS – first–ever haemorrhagic stroke (I60–I62); RHS – recurrent haemorrhagic stroke (I60–I62); ND – no data; [a] – Cochran–Armitage test for trend with Holm–Bonferroni correction

the 3-month recurrence rates are higher for stroke caused by large artery atherosclerosis (14.3%) than for cardioembolic stroke (7.7%), lacunar stroke (2%) and ischaemic stroke due to undetermined causes (5.6%) [27]. A 23-year longitudinal population-based study showed that the implementation of a stroke care network and good primary prevention are defined areas associated with a decrease in the number of recurrent strokes [26].

The clinical symptoms were significantly more expressed in RIS than in FIS. Similarly to other authors, we found that hemiparesis/hemiplegia and speech disorders were the most common presenting symptoms [28].

The median length of hospital stay was 11 (range 9–15) days for RIS and 14 (range 5–24) days for RHS, both shorter than previously described [29]. Hospitalisation time was similar for RIS and FIS, but longer for RHS than for FHS.

Table 5. Median (Q1–Q3) age of patients with stroke in the analysed period

Year	FS	RS	P[a]	FIS	RIS	P[a]	FHS	RHS	P[a]
2009	72 (62–80)	74 (66–81)	< 0.001	73 (63–80)	75 (66–81)	< 0.001	70 (56–78)	73 (63–80)	< 0.001
2010	72 (62–80)	74 (65–81)	< 0.001	73 (62–80)	74 (65–81)	< 0.001	68 (56–79)	72 (62–79)	0.009
2011	73 (62–81)	74 (65–81)	< 0.001	73 (63–81)	74 (65–81)	< 0.001	68 (57–79)	71 (62–80)	0.012
2012	73 (62–81)	74 (65–81)	< 0.001	73 (63–81)	75 (65–81)	< 0.001	67 (56–78)	70 (61–78)	0.004
2013	73 (63–81)	74 (65.5–81)	< 0.001	73 (63–81)	74 (66–82)	< 0.001	70 (59–79)	72 (61–79)	0.139
2014	73 (63–81)	75 (66–82)	< 0.001	73 (64–82)	75 (66–82)	< 0.001	70 (59–79)	73 (64–80)	0.003
2015	73 (63–81)	75 (66–82)	< 0.001	73 (64–81)	75 (67–83)	< 0.001	70 (59–80)	74 (65–80)	0.001
P[b] for trend	< 0.001	< 0.001	–	< 0.001	< 0.001	–	0.001	0.206	–
All	73 (62–81)	74 (66–81)	< 0.001	73 (63–81)	75 (66–81)	< 0.001	69 (57–79)	72 (62–80)	< 0.001

[a] – U Mann–Whitney test;
[b] – Jonckheere–Terpstra test for trend with Holm–Bonferroni correction;
FS – first–ever stroke; RS – recurrent stroke;
FIS – first–ever ischaemic stroke (I63); RIS – recurrent ischaemic stroke (I63);
FHS – first–ever haemorrhagic stroke (I60–I62); RHS – recurrent haemorrhagic stroke (I60–I62)

Table 6. Aetiology of ischaemic stroke in the Silesian Province between 2009 and 2015, according to the TOAST classification

Year		Aetiology of ischaemic stroke					P[a]
		Large–artery atherosclerosis	Cardio––embolism	Small–vessel occlusion (lacune)	Other determined aetiology	Undetermined aetiology	
2009	FIS	2,502 (38.0%)	1,026 (15.6%)	683 (10.4%)	141 (2.1%)	2,232 (33.9%)	< 0.001
	RIS	875 (38.4%)	455 (20.0%)	215 (9.4%)	34 (1.5%)	698 (30.7%)	
2010	FIS	2,672 (36.6%)	1,093 (15.0%)	642 (8.8%)	111 (1.5%)	2,780 (38.1%)	< 0.001
	RIS	912 (38.1%)	463 (19.3%)	177 (7.4%)	35 (1.5%)	810 (33.8%)	
2011	FIS	2,579 (35.3%)	1,348 (18.4%)	699 (9.6%)	110 (1.5%)	2,578 (35.3%)	< 0.001
	RIS	988 (39.3%)	512 (20.3%)	230 (9.1%)	24 (1.0%)	763 (30.3%)	
2012	FIS	2,720 (37.1%)	1,473 (20.1%)	713 (9.7%)	135 (1.8%)	2,298 (31.3%)	0.004
	RIS	943 (38.2%)	555 (22.5%)	187 (7.6%)	49 (2.0%)	735 (29.8%)	
2013	FIS	2,540 (34.5%)	1,395 (19.0%)	778 (10.6%)	126 (1.7%)	2,514 (34.2%)	< 0.001
	RIS	919 (37.9%)	539 (22.3%)	220 (9.1%)	33 (1.4%)	711 (29.4%)	
2014	FIS	2,407 (34.7%)	1,312 (18.9%)	738 (10.6%)	166 (2.4%)	2,314 (33.4%)	0.001
	RIS	824 (38.0%)	454 (20.9%)	211 (9.7%)	35 (1.6%)	645 (29.7%)	
2015	FIS	2,388 (36.2%)	1,276 (19.3%)	675 (10.2%)	125 (1.9%)	2,136 (32.4%)	0.010
	RIS	751 (37.5%)	442 (22.0%)	191 (9.5%)	42 (2.1%)	579 (28.9%)	
P[b] for trend		0.289	< 0.001	0.626	0.751	0.082	–
Total	FIS	17,808 (36.0%)	8,923 (18.1%)	4,928 (10.0%)	914 (1.9%)	16,852 (34.1%)	< 0.001
	RIS	6,212 (38.2%)	3,420 (21.0%)	1,431 (8.8%)	252 (1.6%)	4,941 (30.4%)	

[a] – Chi^2 test with Holm–Bonferroni correction
[b] – Cochran–Armitage test for trend with Holm–Bonferroni correction
FIS – first–ever ischaemic stroke (I63); RIS – recurrent ischaemic stroke (I63)

Table 7. Clinical symptoms of acute stroke in the Silesian Province between 2009 and 2015

	ALL STROKES (I60–I64)	FS (I60–I64)	RS (I60–I64)	P
Consciousness disorders	26,302 (34.4%)	19,301 (33.1%)	7,001 (38.8%)	< 0.001
Hemiparesis/ hemiplegia	61,984 (81.1%)	46,670 (80.0%)	15,314 (84.8%)	< 0.001
Speech disorders	45,117 (59.0%)	33,221 (56.9%)	11,896 (65.9%)	< 0.001
Sensation disorders	25,026 (32.7%)	18,735 (32.1%)	6,291 (34.8%)	< 0.001
Posterior circle syndrome	17,180 (22.5%)	12,943 (22.2%)	4,237 (23.5%)	< 0.001

Table 8. In–hospital mortality in acute first–ever and recurrent stroke in the Silesian Province between 2009 and 2015. Data presented as the number and percentage of deaths, n (%)

Year	Overall hospital mortality in FS	Overall hospital mortality in RS	P FS *vs* RS	Mortality in FIS	Mortality in RIS	P FIS *vs* RIS	Mortality in FHS	Mortality in RHS	P FHS *vs* RHS
2009	1,440 (18.0%)	510 (19.9%)	0.187	954 (14.5%)	396 (17.4%)	0.005	410 (32.8%)	99 (40.2%)	0.166
2010	1,460 (17.0%)	519 (19.4%)	0.033	1,010 (13.8%)	405 (16.9%)	0.002	435 (35.7%)	110 (43.1%)	0.166
2011	1,523 (17.7%)	521 (18.7%)	0.696	1,074 (14.7%)	420 (16.7%)	0.047	422 (34.8%)	93 (38.0%)	1.000
2012	1,468 (16.9%)	491 (18.0%)	0.696	1,004 (13.7%)	395 (16.0%)	0.018	454 (36.0%)	94 (40.3%)	1.000
2013	1,459 (17.0%)	459 (17.2%)	1.000	994 (13.5%)	363 (15.0%)	0.139	452 (38.7%)	87 (39.5%)	1.000
2014	1,342 (16.5%)	432 (17.9%)	0.504	910 (13.1%)	338 (15.6%)	0.018	419 (37.2%)	91 (41.6%)	1.000
2015	1,340 (17.3%)	394 (17.7%)	1.000	939 (14.2%)	318 (15.9%)	0.139	384 (37.0%)	70 (34.8%)	1.000
P[b] for trend	0.261	0.035	–	0.261	0.105	–	0.035	0.0321	–
All	10,032 (17.2%)	3,326 (18.4%)	< 0.001	6,885 (13.9%)	2,635 (16.2%)	< 0.001	2,976 (36.0%)	644 (39.8%)	0.004

FIS – first–ever ischaemic stroke (I63); RIS – recurrent ischaemic stroke (I63);
FHS – first–ever haemorrhagic stroke (I60–I62); RHS – recurrent haemorrhagic stroke (I60–I62)
Data presented as N (%)
[a] – Chi^2 test with Holm–Bonferroni correction
[b] – Cochran–Armitage test for trend with Holm–Bonferroni correction (level of significance for trend in in–hospital mortality between 2009 and 2015)

Table 9. In–hospital mortality in acute first–ever and recurrent stroke in women in the Silesian Province between 2009 and 2015. Data presented as the number and percentage of deaths, n (%)

Year	Overall female hospital mortality in FS	Overall female hospital mortality in RS	P FS *vs* RS	Mortality in FIS	Mortality in RIS	P FIS *vs* RIS	Mortality in FHS	Mortality in RHS	P FHS *vs* RHS
2009	804 (19.8%)	271 (20.3%)	1.000	539 (16.1%)	226 (18.7%)	0.172	220 (35.0%)	42 (36.5%)	1.000
2010	812 (18.2%)	283 (20.3%)	0.499	590 (15.5%)	229 (18.1%)	0.172	215 (35.4%)	52 (46.0%)	0.219
2011	849 (19.3%)	294 (20.4%)	1.000	607 (16.1%)	248 (18.8%)	0.172	219 (37.6%)	41 (38.0%)	1.000
2012	782 (18.3%)	256 (19.0%)	1.000	558 (15.4%)	222 (18.0%)	0.172	218 (36.1%)	34 (32.7%)	1.000
2013	822 (18.3%)	253 (18.5%)	1.000	589 (15.3%)	201 (16.0%)	1.000	226 (38.7%)	47 (48.5%)	0.36
2014	757 (17.8%)	227 (18.8%)	1.000	543 (14.9%)	181 (16.4%)	0.644	204 (36.6%)	44 (46.8%)	0.36
2015	760 (19.4%)	212 (18.8%)	1.000	549 (16.3%)	169 (16.7%)	1.000	202 (39.5%)	40 (38.1%)	1.000
P[b] for trend	0.977	0.492	–	1.000	0.202	–	0.492	1.000	–
All	5,586 (18.7%)	1,796 (19.5%)	0.098	3,975 (15.6%)	1,476 (17.6%)	< 0.001	1,504 (36.9%)	300 (40.8%)	0.046

FIS – first–ever ischaemic stroke (I63); RIS – recurrent ischaemic stroke (I63);
FHS – first–ever haemorrhagic stroke (I60–I62); RHS – recurrent haemorrhagic stroke (I60–I62)
Data presented as N (%)
[a] – Chi^2 test with Holm–Bonferroni correction
[b] – Cochran–Armitage test for trend with Holm–Bonferroni correction (level of significance for trend in in–hospital mortality between 2009 and 2015)

Table 10. In–hospital mortality in acute first–ever and reccurent stroke in men in the Silesian Province between 2009 and 2015. Data presented as the number and percentage of deaths, n (%)

Year	Overall male hospital mortality in FS	Overall male hospital mortality in RS	P[a] FS *vs* RS	Mortality in FIS	Mortality in RIS	P FIS *vs* RIS	Mortality in FHS	Mortality in RHS	P FHS *vs* RHS
2009	636 (16.2%)	239 (19.6%)	0.043	415 (12.8%)	170 (15.9%)	0.053	190 (30.5%)	57 (43.5%)	0.029
2010	648 (15.7%)	236 (18.3%)	0.158	420 (12.1%)	176 (15.5%)	0.016	220 (36.0%)	58 (40.8%)	1.000
2011	674 (16.0%)	227 (16.9%)	0.921	467 (13.2%)	172 (14.3%)	0.296	203 (32.3%)	52 (38.0%)	1.000
2012	629 (15.5%)	217 (17.3%)	0.552	410 (12.0%)	159 (14.1%)	0.143	216 (35.7%)	56 (47.1%)	0.116
2013	637 (15.5%)	206 (15.8%)	0.921	405 (11.6%)	162 (13.9%)	0.102	226 (38.6%)	40 (32.5%)	1.000
2014	585 (15.1%)	205 (17.0%)	0.496	367 (11.2%)	157 (14.7%)	0.013	215 (37.9%)	47 (37.6%)	1.000
2015	580 (15.3%)	182 (16.6%)	0.879	390 (12.1%)	149 (15.0%)	0.061	182 (34.5%)	30 (31.3%)	1.000
P[b] for trend	0.267	0.165	–	0.198	0.400	–	0.165	0.198	–
All	4,389 (15.6%)	1,512 (17.4%)	< 0.001	2,874 (12.1%)	1,145 (14.8%)	< 0.001	1,452 (35.0%)	340 (39.0%)	0.028

FIS – first–ever ischaemic stroke (I63); RIS – recurrent ischaemic stroke (I63);
FHS – first–ever haemorrhagic stroke (I60–I62); RHS – recurrent haemorrhagic stroke (I60–I62)
Data presented as N (%)
[a] – Chi^2 test with Holm–Bonferroni correction
[b] – Cochran–Armitage test for trend with Holm–Bonferroni correction (level of significance for trend in in–hospital mortality between 2009 and 2015)

Table 11. Hospitalisation time of patients with first–ever and recurrent stroke in the Silesian Province between 2009 and 2015. Data presented as median (Q1–Q3) in days

Year	FS	RS	p[a]	FIS	RIS	p[a]	FHS	RHS	p[a]
2009	11 (9–17)	11 (9–17)	0.463	11 (9–16)	11 (9–16)	0.692	13 (3–25)	14 (6–27)	0.047
2010	11 (9–17)	11 (9–16)	0.347	11 (9–16)	11 (9–16)	0.564	14 (3–25)	13 (4–22)	0.453
2011	11 (9–16)	11 (9–17)	0.161	11 (9–15)	11 (9–16)	0.374	13 (3–24)	15 (5–24)	0.134
2012	11 (9–16)	11 (9–15)	0.934	10 (9–15)	11 (9–15)	0.935	12 (3–23)	12 (5–23)	0.366
2013	11 (9–15)	11 (9–15)	0.439	10 (9–15)	11 (9–15)	0.482	13 (3–23)	13 (4–24)	0.197
2014	11 (9–16)	11 (9–16)	0.112	11 (9–15)	11 (9–15)	0.255	14 (4–24)	15 (8–24)	0.073
2015	10 (9–15)	11 (9–15)	0.252	10 (9–14)	10 (9–15)	0.724	12 (3–22)	15 (5–22)	0.151
P[b]	< 0.001	0.116	–	< 0.001	0.015	–	0.946	0.946	–
All	11 (9–16)	11 (9–16)	0.073	11 (9–15)	11 (9–15)	0.437	13 (3–24)	14 (5–24)	0.002

[a] – U Mann–Whitney test
[b] – Jonckheere–Terpstra test for trend with Holm–Bonferroni correction

Table 12. In–hospital mortality in patients treated with intravenous thrombolytic therapy (rt–PA) compared to in–hospital mortality in patients untreated with rt–PA in the Silesian Province between 2009 and 2015

Year	Mortality in FIS treated with rt–PA	Mortality in FIS untreated with rt–PA	P Treated *vs* untreated FIS	Mortality in RIS treated with rt–PA	Mortality in RIS untreated with rt–PA	P Treated *vs* untreated RIS	P Treated FIS *vs* treated RIS
2009	21 (23.9%)	933 (14.4%)	0.071	3 (17.6%)	393 (17.4%)	1.000	1.000
2010	23 (14.0%)	987 (13.8%)	1.000	4 (14.8%)	401 (16.9%)	1.000	1.000
2011	33 (13.6%)	1,041 (14.7%)	1.000	7 (14.0%)	413 (16.7%)	1.000	1.000
2012	53 (14.5%)	951 (13.6%)	1.000	13 (15.9%)	382 (16.0%)	1.000	1.000
2013	56 (12.8%)	938 (13.6%)	1.000	12 (14.3%)	351 (15.0%)	1.000	1.000
2014	104 (16.8%)	806 (12.8%)	0.033	21 (16.0%)	317 (15.6%)	1.000	1.000
2015	106 (15.6%)	833 (14.1%)	1.000	27 (20.1%)	291 (15.6%)	1.000	1.000
P[a] for trend	0.982	0.173	–	0.739	0.060	–	–
All	396 (15.2%)	6,489 (13.9%)	0.142	87 (16.6%)	2,548 (16.2%)	0.885	0.885

[a] – Chi^2 test with Holm–Bonferroni correction

Table 13. Comparison of in–hospital mortality in men treated with intravenous thrombolytic therapy (rt–PA) to in–hospital mortality in women treated with rt–PA in the Silesian Province between 2009 and 2015

Year	Mortality in men in FIS treated with rt–PA	Mortality in women in FIS treated with rt–PA	P F *vs* M	Mortality in men in RIS treated with rt–PA	Mortality in women in RIS treated with rt–PA	P F *vs* M
2009	9 (22.0%)	12 (25.5%)	1.000	3 (30.0%)	0 (0%)	0.772
2010	13 (14.3%)	10 (13.7%)	1.000	1 (10.0%)	3 (17.6%)	1.000
2011	22 (15.8%)	11 (10.7%)	1.000	3 (12.5%)	4 (15.4%)	1.000
2012	26 (13.9%)	24 (15.2%)	1.000	8 (17.8%)	5 (16.1%)	1.000
2013	24 (10.5%)	32 (15.2%)	0.949	4 (9.8%)	8 (18.6%)	1.000
2014	55 (16.9%)	49 (16.6%)	1.000	9 (13.6%)	12 (18.5%)	1.000
2015	52 (15.3%)	54 (15.9%)	1.000	18 (24.7%)	9 (14.8%)	0.928
P[a] for trend	1.000	1.000	–	1.000	1.000	–
All	201 (14.9%)	192 (15.7%)	0.570	46 (17.1%)	41 (16.4%)	0.831

[a] – Chi^2 test with Holm–Bonferroni correction

Table 14. In–hospital mortality (n, %) in association with the aetiology of FIS in the Silesian Province between 2009 and 2015

Year	Atiology of ischaemic stroke					P[a]
	Large–artery atherosclerosis	Cardio–embolism	Small–vessel occlusion (lacune)	Other determined aetiology	Undetermined aetiology	
2009	344 (13.8%)	196 (19.1%)	15 (2.2%)	18 (12.8%)	381 (17.1%)	< 0.001
2010	359 (13.4%)	194 (17.8%)	22 (3.4%)	13 (11.7%)	422 (15.2%)	< 0.001
2011	327 (12.7%)	299 (22.2%)	32 (4.6%)	15 (13.6%)	401 (15.6%)	< 0.001
2012	375 (13.8%)	262 (17.8%)	31 (4.4%)	13 (9.6%)	323 (14.1%)	< 0.001
2013	338 (13.3%)	262 (18.8%)	47 (6%)	6 (4.8%)	341 (13.6%)	< 0.001
2014	287 (11.9%)	233 (17.8%)	36 (4.9%)	14 (8.4%)	340 (14.7%)	< 0.001
2015	330 (13.8%)	226 (17.7%)	48 (7.1%)	20 (16.0%)	315 (14.8%)	< 0.001
P[b] for trend	1.000	0.468	< 0.001	1.000	0.045	–
Total	2.360 (13.3%)	1.672 (18.7%)	231 (4.7%)	99 (10.8%)	2.523 (15%)	< 0.001

[a] – Chi^2 test with Holm–Bonferroni correction
[b] – Cochran–Armitage test for trend with Holm–Bonferroni correction

Table 15. In–hospital mortality (n, %) in association with the aetiology of RIS in the Silesian Province between 2009 and 2015

Year	Aetiology of ischaemic stroke					P[a]
	Large–artery atherosclerosis	Cardio–embolism	Small–vessel occlusion (lacune)	Other determined aetiology	Undetermined aetiology	
2009	159 (18.2%)	88 (19.3%)	13 (6.1%)	2 (5.9%)	134 (19.2%)	< 0.001
2010	148 (16.2%)	100 (21.6%)	15 (8.5%)	4 (11.4%)	138 (17.0%)	0.004
2011	159 (16.1%)	112 (21.9%)	16 (7.0%)	3 (12.5%)	130 (17.0%)	< 0.001
2012	145 (15.4%)	114 (20.5%)	12 (6.4%)	7 (14.3%)	117 (15.9%)	0.001
2013	131 (14.3%)	98 (18.2%)	15 (6.8%)	3 (9.1%)	116 (16.3%)	0.004
2014	148 (18.0%)	85 (18.7%)	15 (7.1%)	7 (20.0%)	83 (12.9%)	0.001
2015	119 (15.9%)	83 (18.8%)	18 (9.4%)	9 (21.4%)	89 (15.4%)	0.043
P[b] for trend	0.795	0.720	0.795	0.168	0.031	–
Total	1009 (16.2%)	680 (19.9%)	104 (7.3%)	35 (13.9%)	807 (16.3%)	< 0.001

[a] – Chi^2 test with Holm–Bonferroni correction
[b] – Cochran–Armitage test for trend with Holm–Bonferroni correction

Table 16. In–hospital mortality in patients treated with rt–PA (n, %) in association with the aetiology of first–ever ischaemic stroke (I63; n=49,452) in the Silesian Province between 2009 and 2015

Year	Aetiology of ischaemic stroke					Pa
	Large–artery atherosclerosis	Cardio–embolism	Small–vessel occlusion (lacune)	Other determined aetiology	Undetermined aetiology	
2009	11 (36.7%)	2 (11.1%)	0 (0%)	0 (0%)	8 (22.2%)	0.657
2010	8 (11.6%)	5 (15.2%)	0 (0%)	0 (0%)	10 (20.4%)	1.000
2011	12 (15.6%)	11 (17.5%)	1 (4.8%)	0 (0%)	9 (11.4%)	1.000
2012	18 (16.5%)	18 (16.2%)	2 (7.7%)	0 (0%)	15 (13.3%)	1.000
2013	15 (11.1%)	18 (13.5%)	2 (7.1%)	0 (0%)	21 (15.1%)	1.000
2014	32 (15.3%)	41 (23.6%)	6 (12.5%)	1 (14.3%)	24 (13.2%)	0.545
2015	32 (13.5%)	26 (14.1%)	4 (8.3%)	2 (28.6%)	42 (20.9%)	0.545
P[b] for trend	0.505	1.000	0.681	0.290	1.000	–
Total	128 (14.8%)	121 (16.9%)	15 (8.2%)	3 (9.7%)	129 (16.2%)	0.040

[a] – Chi^2 test with Holm–Bonferroni correction
[b] – Cochran–Armitage test for trend with Holm–Bonferroni correction

Table 17. In–hospital mortality in patients treated with rt–PA (n, %) in association with the aetiology of RIS in the Silesian Province between 2009 and 2015

Year	Aetiology of ischaemic stroke					P[a]
	Large–artery atherosclerosis	Cardio–embolism	Small–vessel occlusion (lacune)	Other determined aetiology	Undetermined aetiology	
2009	1 (14.3%)	1 (50%)	0 (0%)	0 (0%)	1 (14.3%)	1.000
2010	3 (25%)	0 (0%)	0 (0%)	0 (0%)	1 (11.1%)	1.000
2011	3 (15.8%)	2 (12.5%)	0 (0%)	0 (0%)	2 (22.2%)	1.000
2012	6 (19.4%)	3 (17.7%)	0 (0%)	0 (0%)	4 (13.3%)	1.000
2013	5 (13.5%)	5 (25%)	0 (0%)	0 (0%)	2 (8%)	1.000
2014	10 (18.9%)	8 (19.5%)	0 (0%)	1 (50%)	2 (7.1%)	1.000
2015	9 (17.7%)	4 (13.8%)	4 (28.6%)	0 (0%)	10 (26.3%)	1.000
P[b] for trend	1.000	1.000	0.419	1.000	1.000	–
Total	37 (17.6%)	23 (17.7%)	4 (13.3%)	1 (11.1%)	22 (15.1%)	0.918

[a] – Chi^2 test with Holm–Bonferroni correction
[b] – Cochran–Armitage test for trend with Holm–Bonferroni correction

Table 18. Secondary stroke prevention in patients with ischaemic stroke (I63) in the Silesian Province between 2009 and 2015. Data presented as N (%)

Year		Oral antiplatelet drugs	Oral anticoagulant drugs	Antihypertensive drugs	Direction for vascular intervention due to artery stenosis[b]
2009	All	7,303 (78.7%)	2,194 (23.7%)	7,095 (76.5%)	202 (2.2%)
	FIS	5,267 (80.0%)	1,511 (22.9%)	4,924 (74.8%)	162 (2.5%)
	RIS	1,760 (77.3%)	605 (26.6%)	1,869 (82.1%)	38 (1.7%)
2010	All	8,383 (83.3%)	2,650 (26.3%)	7,939 (78.9%)	350 (3.5%)
	FIS	6,177 (84.6%)	1,879 (25.7%)	5,678 (77.8%)	272 (3.7%)
	RIS	1,939 (80.9%)	722 (30.1%)	1,994 (83.2%)	71 (3.0%)
2011	All	8,535 (83.5%)	2,608 (25.5%)	8,233 (80.5%)	315 (3.1%)
	FIS	6,191 (84.6%)	1,846 (25.2%)	5,862 (80.1%)	230 (3.1%)
	RIS	2,054 (81.6%)	694 (27.6%)	2,086 (82.9%)	80 (3.2%)
2012	All	8,655 (85.0%)	2,593 (25.5%)	8,193 (80.4%)	379 (3.7%)
	FIS	6,272 (85.5%)	1,805 (24.6%)	5,816 (79.2%)	278 (3.8%)
	RIS	2,087 (84.5%)	719 (29.1%)	2,079 (84.2%)	95 (3.8%)
2013	All	8,682 (84.4%)	2,301 (22.4%)	8,331 (81.0%)	344 (3.3%)
	FIS	6,245 (84.9%)	1,588 (21.6%)	5,912 (80.4%)	264 (3.6%)
	RIS	2,020 (83.4%)	579 (23.9%)	2,031 (83.9%)	68 (2.8%)
2014	All	8,248 (83.7%)	1,965 (19.9%)	8,187 (83.1%)	344 (3.5%)
	FIS	5,909 (85.2%)	1,380 (19.9%)	5,820 (83.9%)	249 (3.6%)
	RIS	1,794 (82.7%)	480 (22.1%)	1,890 (87.1%)	86 (4.0%)
2015	All	7,830 (82.2%)	1,888 (19.8%)	7,993 (84.0%)	326 (3.4%)
	FIS	5,605 (84.9%)	1,335 (20.2%)	5,483 (83.1%)	241 (3.7%)
	RIS	1,631 (81.3%)	459 (22.9%)	1,773 (88.4%)	72 (3.6%)
P[a] for trend	All	< 0.001	< 0.001	< 0.001	< 0.001
	FIS	< 0.001	< 0.001	< 0.001	0.002
	RIS	< 0.001	< 0.001	< 0.001	< 0.001
ALL	All	57,636 (83.0%)	16,199 (23.3%)	55,971 (80.6%)	2,260 (3.2%)
	FIS	41,666 (84.3%)	11,344 (23.0%)	39,495 (79.9%)	1,696 (3.4%)
	RIS	13,285 (81.7%)	4,258 (26.2%)	13,722 (84.4%)	510 (3.1%)

[a] – Trend test Cochran–Armitage with Holm–Bonferroni correction
[b] – endarterectomy or angioplasty of cervical artery

Table 19. Secondary stroke prevention in patients with ischaemic stroke (I63) with cardioembolic aetiology in the Silesian Province between 2009 and 2015. Data presented as N (%)

Year		Oral antiplatelet drugs	Oral anticoagulant drugs
2009	All	1,081 (68.9%)	589 (37.6%)
	FIS	734 (71.5%)	385 (37.5%)
	RIS	296 (65.1%)	183 (40.2%)
2010	All	1,203 (74.2%)	604 (37.2%)
	FIS	819 (74.9%)	415 (38.0%)
	RIS	340 (73.4%)	180 (38.9%)
2011	All	1,402 (72.5%)	697 (36.1%)
	FIS	982 (72.8%)	503 (37.3%)
	RIS	373 (72.9%)	180 (35.2%)
2012	All	1,545 (73.9%)	766 (36.7%)
	FIS	1091 (74.1%)	519 (35.2%)
	RIS	404 (72.8%)	234 (42.2%)
2013	All	1,445 (71.4%)	739 (36.5%)
	FIS	989 (70.9%)	488 (35.0%)
	RIS	389 (72.2%)	211 (39.1%)
2014	All	1,240 (65.7%)	774 (41.0%)
	FIS	875 (66.7%)	536 (40.9%)
	RIS	284 (62.6%)	207 (45.6%)
2015	All	1,155 (62.5%)	734 (39.7%)
	FIS	821 (64.3%)	497 (38.9%)
	RIS	271 (61.3%)	195 (44.1%)
P[a] for trend	All	< 0.001	< 0.001
	FIS	< 0.001	0.253
	RIS	0.004	0.033
ALL	All	9,071 (69.9%)	4,903 (37.8%)
	FIS	6,311 (70.7%)	3,343 (37.5%)
	RIS	2357 (68.9%)	1,390 (40.6%)

[a] — Trend test Cochran–Armitage with Holm–Bonferroni correction

Lekoubou et al. observed that stroke survivors had a 43% higher risk of dying after a RS compared to those with FS, because of unfavourable stroke risk profile [30]. In our study, the in-hospital mortality rate was also significantly higher for RS than for FS (18.4% *vs* 17.2%; p < 0.001). The same finding concerned RIS *vs* FIS (16.2% *vs* 13.9%; p < 0.001), and RHS *vs* FHS (39.8% *vs* 36%; p = 0.004). This might be also associated with older age and more expressed clinical symptoms in patients with RS.

We found that the rtPA therapy was applied to a smaller percentage of RIS patients (in 2009 – 0.7%; in 2015 – 6.7%) than FIS patients (in 2009 – 1.3%; in 2015 – 10.3%).

In some Western European countries, the percentage of patients with IS treated with rtPA was higher than in the Silesian Province e.g. up to 35% in the German state of Hesse (2007–2008) [31–33]. Silesia has a dense urban infrastructure and the densest hospital network in Poland, so transportation seems not to be a problem. In our opinion, the main reason for the low percentage of patients treated with rtPA in the Silesian Province remains insufficient knowledge and social awareness of stroke symptoms and the possibilities of treatment [34, 35]. Educational programmes should be regularly conducted among people using all forms of modern media.

Conclusions

1. Recurrent strokes constituted about one fifth of all stroke hospitalisations. However, the recurrence rate of ischaemic stroke has systematically decreased over the last decade. This is evidence of better secondary stroke prevention.
2. Large-artery atherosclerosis and cardioembolisms were significantly more often recognised in RIS than in FIS, but the main reason for RIS was large artery atherosclerosis.
3. The in-hospital mortality rate was significantly higher for RS than for FS.
4. Patients with RIS were almost two times less often treated with rtPA than patients with FIS.
5. This was the first such comprehensive analysis of RS in the Silesian Province, Poland. This study could help in the implementation of appropriate educational programmes, and thus help to improve the health status of society.

Limitations of the study

There were a few limitations to this research, as described in previous studies [15, 16]. Firstly, in our paper we analysed only stroke-related hospitalisations, but in Poland almost all patients with AS are admitted to hospital. Secondly, it is possible that in the case of some ASs the questionnaires might not have been sent to the NHF. Thirdly, we could not estimate the number of stroke-related deaths that had occurred prior to the patient's arrival at hospital, and therefore the true hospitalised incidence of stroke might be underestimated. Fourthly, we only analysed the questionnaire data and the information those questionnaires contained. As a result, human error could have occurred. Fifthly, the data was anonymous so we could not analyse the trends for strokes.

Acknowledgments

The authors wish to thank Professor Krystyna Pierzchala, MD, PhD, the former Consultant in Neurology for the Silesian Province, for supporting the initiative of the epidemiological study on stroke in the Silesian Province.

Funding: *None declared.*
Conflict of interest: *None declared.*

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RESEARCH PAPER

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2019, Volume 53, no. 4, pages: 291–295
DOI: 10.5603/PJNNS.a2019.0036

ISSN 0028–3843

A new therapeutic strategy with istradefylline for postural deformities in Parkinson's disease

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ABSTRACT

Aim of the study. Postural deformities are common in Parkinson's disease (PD) patients. Several treatment options have been reported, but responses to these treatments appear unpredictable. Istradefylline is a novel drug for PD. Cases of PD patients whose postural deformities were improved after withdrawal of dopamine agonists and initiation of istradefylline are presented.

Materials and methods. Four consecutive patients with postural deformities including antecollis, Pisa syndrome, and camptocormia were recruited and treated with istradefylline in combination with withdrawal of dopamine agonists, which are possible causes of postural deformities.

Results. The dopamine agonists were discontinued an average of 26 months after the development of the postural deformities, and istradefylline was initiated an average of 1.3 months after dopamine agonist withdrawal. Three patients with preserved paraspinal muscle volume showed good responses to the treatment regimen at least two months after dopamine agonist withdrawal.

Conclusions and clinical implications. Postural deformities caused by dopamine agonists generally improve less than two weeks after dopamine agonist withdrawal. Given the response time in the present study, the response was unlikely to be caused solely by dopamine agonist withdrawal. Istradefylline can be a potential therapeutic option; however, appropriate selection of patients for treatment with istradefylline is warranted.

Key words: Parkinson's disease, istradefylline, postural deformity, camptocormia, antecollis, Pisa syndrome

(*Neurol Neurochir Pol 2019; 53 (4): 291–295***)**

Introduction

Patients with Parkinson's disease (PD) often develop postural deformities including camptocormia, antecollis, Pisa syndrome, and scoliosis [1]. Possible pathophysiological mechanisms for postural deformities, such as dystonia, rigidity, myopathy, impaired proprioception, spine structural changes, and impaired spatial perception, have been proposed [1]. Postural deformities can be induced by several drugs, including amantadine, levodopa, and valproic acid. Dopamine agonists can also induce postural deformities, and withdrawal of the dopamine agonist alone may lead to prompt symptom relief. However, withdrawal of the dopamine agonist may worsen the motor symptoms of PD. Other treatment options including deep brain stimulation and botulinum toxin injection are available, but they are unsatisfactory in some patients [2]. Istradefylline, an adenosine A2A receptor antagonist, is a novel non-dopaminergic drug available for the treatment of

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PD in Japan [3]. A clinical trial of istradefylline for PD patients showed reduced off time and improved Unified Parkinson's Disease Rating Scale motor scores. However, a 12-week, double-blind study to assess the efficacy of istradefylline failed to prove efficacy in improving motor symptoms [4]. The detailed pharmacokinetics of istradefylline are unknown.

Very recently, Suzuki et al. reported that nine of 18 PD patients with postural abnormalities who were treated with istradefylline showed a significant improvement ($p < 0.05$) in posture, as assessed using the sub-score for posture on the Movement Disorder Society revision of the Unified Parkinson's Disease Rating Scale part III [5]. Possible mechanisms underlying the response to the therapy have been previously suggested [6]. Postural deformity can be caused by dystonia, and blockade of A2A receptors was shown to restore the impairment of synaptic plasticity in dystonia mice. Another potential mechanism is that an inadequate dose of anti-parkinsonian drugs could be one of the causes of postural deformity that can be ameliorated by istradefylline, which can decrease the off-periods [7].

However, that study did not clarify which factors affect response. In addition, the clinical details of each patient were not described in that report. The cases of four PD patients with postural deformities who were treated with istradefylline in combination with dopamine agonist withdrawal are here presented. Three patients showed improvements in postural deformities without deterioration of motor function. The details of the patients' clinical disease courses are presented, along with the possible predictors of postural improvement with istradefylline.

Materials and methods

The clinical charts of 103 PD patients who visited the Department of Neurology at our hospital between 1 April, 2015 and 31 March, 2016 were reviewed, and four PD patients with postural deformities were identified. Treatment with istradefylline was then begun after obtaining their informed consent for treatment. The clinical diagnosis of PD was made by board-certified neurologists (SF, TM, JF, YT) according to the UK Brain Bank Clinical Diagnostic Criteria [8]. Patients with previous spinal bone fractures were excluded, as were patients who had mild postural deformities that did not impact upon daily life. Data on demographics and clinical and magnetic resonance imaging (MRI) findings for patients treated with istradefylline were retrieved.

All experimental procedures were conducted in accordance with the policies and ethical principles of the Declaration of Helsinki. This study was approved by the Ethics Committee of our institution.

Results

The patients' mean age at PD onset and mean disease duration were 69 (standard deviation (SD) 7.0) years and 5 (SD 0.5) years, respectively. The mean Hoehn and Yahr stage was approximately 3. The detailed clinical courses of the four patients are presented below.

Patient 1 developed clumsiness in the upper right limb at 73 years of age. She was diagnosed with PD and started on ropinirole at 74 years, with amelioration of her symptoms. She began to take levodopa at 76 years. She showed a forward-bent posture that had gradually worsened, and she also developed a dropped head during the disease course (Fig. 1A). Zonisamide and selegiline were added during the disease course, but the postural deformity did not respond to the medication. Neurological examination showed camptocormia and antecollis. Ropinirole was withdrawn, and istradefylline (40 mg/day) was simultaneously started at 77 years. Two months after the initiation of istradefylline, the postural abnormalities gradually improved, and she showed normal posture for an elderly person three months after beginning istradefylline (Fig. 1B, C). MRI showed good preservation of paraspinal muscle volume (Fig. 1D-G).

Patient 2 presented with a gait disturbance at 72 years of age and was diagnosed with PD at 74 years. She started taking levodopa, and pramipexole was subsequently added, which improved her parkinsonism considerably. She developed a dropped head at 74 years (Fig. 1H). Selegiline and entacapone were added at 74 and 75 years, respectively. Pramipexole was changed to ropinirole at 76 years. Botulinum toxin injection for the sternocleidomastoid muscles did not improve her symptoms at the age of 77 years. On neurological examination, she had camptocormia and antecollis, and ropinirole was discontinued at 79 years. Two months after discontinuation of ropinirole, istradefylline (40 mg/day) was started. Two months after the initiation of istradefylline, postural abnormalities showed gradual improvement, and normal posture for an elderly person was restored three months after beginning istradefylline (Fig. 1I, J). MRI showed mild paraspinal muscle atrophy (Fig. 1K-N).

Patient 3 developed a tremor in the upper right limb at 62 years of age. She was diagnosed with PD at 63 years. She was first given levodopa, which ameliorated her parkinsonism. She started to take rotigotine and amantadine during the course of the illness. She developed lateral trunk flexion at 66 years, with gradual deterioration (Fig. 1O). On examination, she showed Pisa syndrome. Rotigotine was withdrawn, and zonisamide and trihexyphenidyl were added, but the symptoms did not improve. One month after withdrawal of rotigotine, istradefylline (40 mg/day) was started. Six months after initiating istradefylline, her postural abnormalities were mildly improved (Fig. 1P). MRI showed mild atrophy of the paraspinal muscles (Fig. 1Q-T).

Patient 4 developed a resting tremor and motor slowness in the lower left limb at 59 years. She was diagnosed with PD at 60 years, and she started taking levodopa and pramipexole, which improved her symptoms. She presented with a dropped head at 67 years. Despite adjustment of anti-parkinsonian drugs, parkinsonism and the dropped head gradually

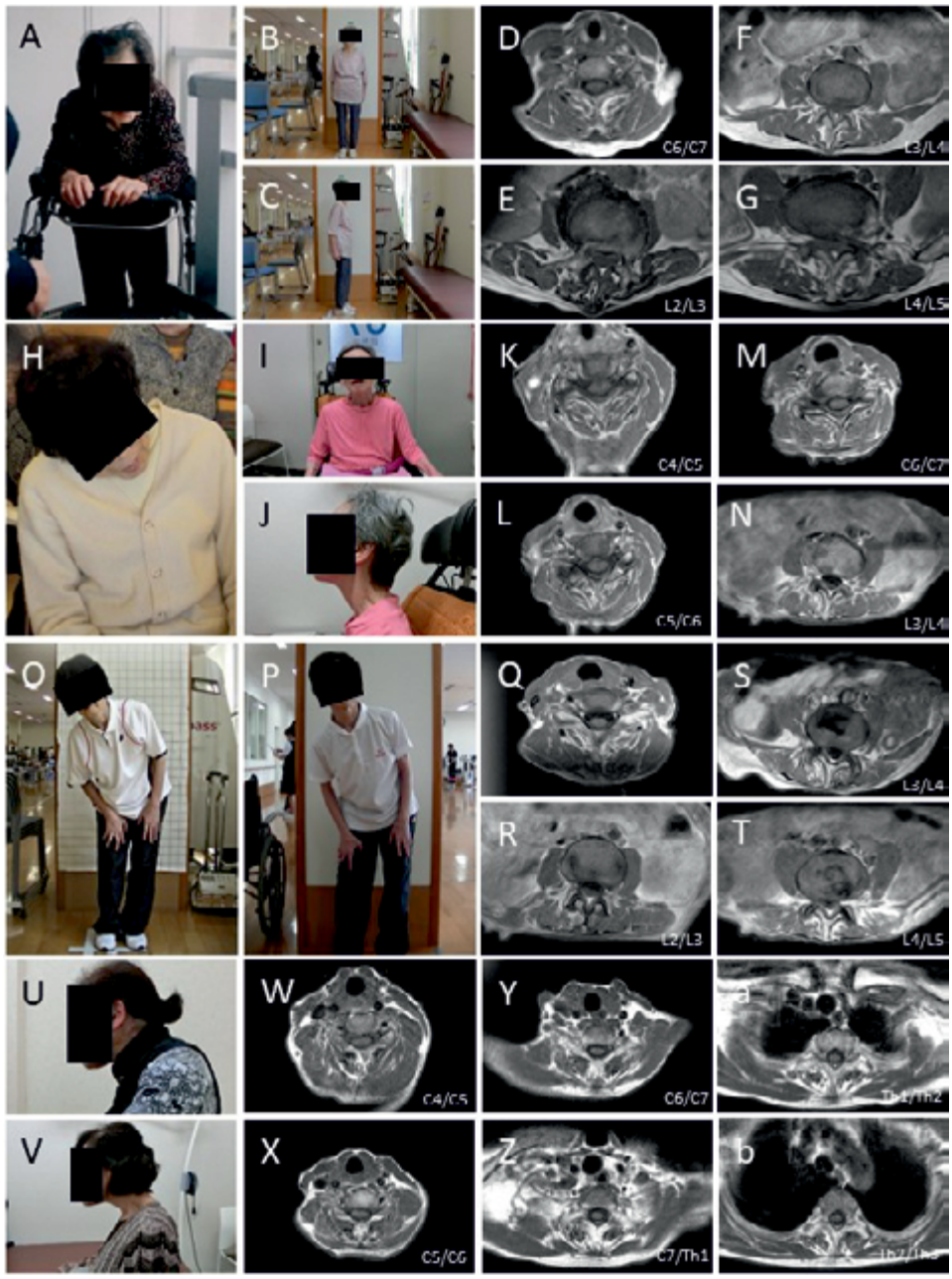

Figure 1. Description of patients before and after initiation of istradefylline and MRI observations.
Patient 1 presented with camptocormia and antecollis (A), which improved greatly after initiation of istradefylline (B, C). MRI T1WI (D-G) shows well-preserved paraspinal muscle volume. Patient 2 showed antecollis (H) that improved greatly three months after initiation of istradefylline (I, J). Patient 3 showed Pisa syndrome (O), which was partially ameliorated after initiation of istradefylline (P). MRI T1WI examinations of both patients (K-N: Patient 2; Q-T: Patient 3) show relatively preserved paraspinal muscle volume. Patient 4 showed antecollis (U) and experienced no improvement after initiation of istradefylline (V). MRI T1WI examination of Patient 4 (W-Z, a, b) shows moderate atrophy of the paraspinal muscles

worsened (Fig. 1U). On neurological examination, she had antecollis; the pramipexole was reduced, and istradefylline was started at 70 years. Pramipexole was withdrawn two months before starting istradefylline (40 mg/day). However, even eight months after initiation of istradefylline, the dropped head had not improved (Fig. 1V). MRI (T1WI) showed moderate atrophy of the paraspinal muscles (Fig. 1W-Z, 1a, 1b).

The demographic and clinical data of the patients are set out in Table 1.

Discussion

The clinical courses of four PD patients with postural deformities who were treated with istradefylline in combination

Table 1. Summary of demographic and clinical data of four PD patients with postural deformities

Patient	AAO (years)	DD (years)	H&Y stage	Type of postural deformities	Combined medications before initiation of istradefylline (/day)	Period A (months)	Period B (months)	Period C (months)	Period D (months)
1	73	4	3	Camptocormia, antecollis	Levodopa 300 mg Ropinirole 6 mg Zonisamide 25 mg Selegiline 2.5 mg	8	12	0	2
2	72	7	4	Antecollis	Levodopa 600 mg Ropinirole 8 mg Droxidopa 600 mg	6	60	2	2
3	62	4	3	Pisa syndrome	Levodopa 200 mg Rotigotine 18 mg Amantadine 100 mg	10	6	1	6
4	59	11	3	Antecollis	Levodopa 450 mg Pramipexole 8 mg Zonisamide 25 mg	84	36	2	NA

AAO – age at onset; DD – disease duration; H&Y – Hoehn & Yahr; NA – not applicable;
Period A – period between initiation of dopamine agonist and onset of postural deformities;
Period B – period between onset of postural deformities and withdrawal of dopamine agonist;
Period C – period between withdrawal of dopamine agonist and initiation of istradefylline;
Period D – period between initiation of istradefylline and improvement of postural deformities

with the withdrawal of dopamine agonists are here presented. Patient 1 showed camptocormia and antecollis, Patient 2 showed antecollis, Patient 3 showed Pisa syndrome, and Patient 4 had antecollis. All patients had initially been treated with levodopa/carbidopa and a dopamine agonist before the development of postural deformities. One of the most common causes of postural deformities seen in PD is medications, especially dopamine agonists. Thus, the dopamine agonists were stopped, and the patients were treated with istradefylline during the disease course to avoid deterioration of motor function. For Patient 1, istradefylline was started at the same time as dopamine agonist withdrawal. For the other patients, istradefylline was initiated at least two months after dopamine agonist withdrawal. Three of the four PD patients showed clinical improvement of postural deformities at least two months after dopamine agonist withdrawal. Postural deformities caused by dopamine agonist medications generally improve relatively quickly (≤ 2 weeks after dopamine agonist withdrawal). Given the response time seen in the presented patients, the clinical response was unlikely to have been caused solely by dopamine agonist withdrawal. In addition, a very recent report by Suzuki et al. showed improvements in postural deformities with istradefylline treatment [5].

Paraspinal muscle volume is considered to predict improvement of postural deformities by deep brain stimulation. Saki et al. performed subthalamic deep brain stimulation in 14 PD patients with camptocormia and showed significantly higher paraspinal muscle volume in patients who responded well to therapy compared to those who showed partial or no response [9]. In the presented cases, MRI showed preservation of paraspinal muscle volume in Patients 1–3, who showed good to mild improvement with istradefylline, whereas Patient 4, who showed no clinical improvement, showed moderate atrophy of the paraspinal muscles. As for deep brain stimulation, paraspinal muscle volume is a potentially good predictor of success when treating postural deformities in PD with istradefylline.

The exact pharmacokinetics of adenosine A2A receptor blockade remain unclear. Dystonia is one cause of postural deformities. Napolitano et al. reported that adenosine A2A receptor blockade rescues physiological synaptic plasticity, leading to an improved phenotype in DYT1 mutant mice [10]. The pedunculo-pontine tegmental nucleus is associated with muscle tone control. Another potential mechanism is that adenosine A2A receptor blockade by istradefylline inhibits basal ganglia output through an indirect pathway that leads to amelioration of excess inhibition of this nucleus [11].

One limitation of this study was the absence of quantitative evaluation of postural deformities. Another limitation is the absence of strategic methods for MRI acquisition to assess muscle volume. In addition, due to the retrospective nature of this study, some clinical information was missing.

Clinical implications/future directions

Postural deformities greatly impair patients' activities of daily living and unquestionably lead to worsening of their quality of life; therefore, novel therapies are needed. Given the limited availability of pharmacological agents for postural

deformities, istradefylline is a potential therapeutic option. Dopamine agonist withdrawal may lead not only to an improvement in postural deformity, but also to a deterioration of parkinsonism. Conversion from a dopamine agonist to istradefylline is potentially safe and beneficial for patients with postural deformities, without leading to deterioration of motor symptoms.

Acknowledgement

The authors would like to thank the staff at Fukuoka University Hospital for their kind support and for the management of patients.

Funding: *This publication was prepared without any external sources of funding.*
Conflict of interest: *None.*

Author contributions

All authors contributed substantially to this study: conception and design of the study (S.F., Y.T.); acquisition and interpretation of data (S.F., R.Y., K.N., Y.T.); drafting of the article (S.F.); revising the article critically for important intellectual content (R.Y., K.N., H.Y., T.M., J.F., K.K., H.K., Y.T.); and final approval of the version to be submitted (S.F., R.Y., K.N., H.Y., T.M., J.F., K.K., H.K., Y.T.).

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RESEARCH PAPER

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2019, Volume 53, no. 4, pages: 296–303
DOI: 10.5603/PJNNS.a2019.0029

ISSN 0028–3843

Risk factors predicting a higher grade of subarachnoid haemorrhage in small ruptured intracranial aneurysm (< 5 mm)

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ABSTRACT

Aim. To identify the risk factors for clinical and radiographic grades of subarachnoid haemorrhage (SAH) in small (< 5 mm) intracranial aneurysms (SIAs).

Material and methods. We retrospectively analysed patients with SIAs treated in our centre between February 2009 and June 2018. The clinical status was graded using the Hunt and Hess (H&H) score and the radiological severity of SAH was graded by Fisher grades (FG). The risk factors were determined using multivariate logistic regression analysis.

Results. A total of 160 patients with ruptured SIAs (< 5 mm) were included. In univariate analysis, smoking (P = 0.007), alcohol use (P = 0.048), aspirin use (P = 0.001), and higher size ratio (SR) (P = 0.001) were significantly associated with a higher H&H grade (3–5) in SIAs; and smoking (P = 0.019), aspirin use (P = 0.031), inflow angle < 90 degrees (P = 0.011), and aneurysm size (P = 0.039) were significantly associated with a higher FG score (3–4). In the adjusted multivariate analysis, previous SAH (OR, 12.245, 95% CI, 2.261–66.334, P = 0.004), aspirin use (OR, 4.677, 95% CI, 1.392–15.718, P = 0.013), alcohol use (OR, 3.392, 95% CI, 1.146–10.045, P = 0.027), inflow angle < 90 (OR, 3.881, 95% CI, 1.273–11.831, P = 0.017), and higher SR (OR, 6.611, 95% CI, 2.235–19.560, P = 0.001) were independent risk factors for a higher H&H grade in ruptured SIAs; smoking (OR, 2.157, 95% CI, 1.061–4.384, P = 0.034), and inflow angle < 90 degrees (OR, 2.603, 95% CI, 1.324–5.115, P = 0.006) were independent risk factors for a higher FG (3–4).

Conclusions. This study revealed that inflow angle < 90 degrees and size ratio, but not absolute size, may highly predict poorer grade of SAH in SRA. Aspirin use, previous SAH, and alcohol use were significantly associated with a higher H&H grade in ruptured SIAs, and smoking was a significant predictor of poorer FG.

Key words: intracranial aneurysm, small, rupture, aspirin use, Hunt and Hess score, Fisher grade

(*Neurol Neurochir Pol 2019; 53 (4): 296–303*)

Introduction

With a 30-day mortality rate of 40%, the most serious damage caused by intracranial aneurysms (IAs) is subarachnoid haemorrhage (SAH) [1–3]. The rupture risk of IAs has been known to increase with increasing aneurysm size. However, some authors have found that the incidence of SAH caused by small aneurysms was increased [4–7], and have clearly demonstrated that approximately 13–50% of ruptured IAs (RIAs) were small (< 5 mm) [8, 9]. As with large aneurysms, the most widely used scales for grading the disease severity of SAH in small (< 5 mm) intracranial aneurysms (SIAs) are the Hunt and Hess (H&H) and the Fisher grades (FG). Many articles have indicated that small aneurysms have different morphological characteristics; however, whether these characteristics are related to the disease severity of SAH is still unclear.

There is a plethora of available literature reporting metabolic indicators as potential markers of the disease severity of an SAH [10, 11]. Although different morphologic parameters such as aspect ratio (AR), size ratio (SR), and inflow angle have been believed to contribute significantly to determining the risk of small aneurysm rupture [9, 12–14], the impact of these morphologic features on the severity of SAH caused by an SRA still remains unexplored.

In addition, antiplatelet agents (aspirin in particular) have emerged as possible options for noninvasive treatment of IAs to decrease the incidence of aneurysmal SAH. On the other hand, according to a meta-analysis of seven studies, aspirin use may be significantly associated with an increased risk of aneurysm rupture [15]. However, the association between aspirin use and the clinical and radiographic grades of SAH caused by SIAs remains unclear.

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For small aneurysms (< 5 mm) that are often considered to be at a low risk of rupture, conservative treatment is generally recommended clinically [8, 9, 12], so small aneurysms are the most likely type of aneurysm to receive conservative observations and protective treatments such as taking aspirin. Therefore, it is important to investigate the risk factors affecting the severity of SAH caused by small aneurysms.

In this study, we aimed to investigate the effects of morphologic parameters and history of aspirin use on clinical and radiographic grades of SAH caused by SIAs.

Material and methods

A total of 160 patients (84 women and 76 men) with ruptured small IAs (SIA) (< 5 mm) who were diagnosed and treated between February 2009 and June 2018 at our centre were retrospectively analysed in this study. The exclusion criteria were as follows: 1) fusiform, mycotic, and traumatic aneurysms; 2) aneurysm diameter ≥ 5 mm; 3) intracranial haemorrhage due to unknown reasons, or inability to identify the location of the ruptured aneurysm among multiple IAs; 4) inability to evaluate aneurysm geometry and morphology with computed tomography angiography/ /digital subtraction angiography (CTA/DSA); and 5) patients who presented other cerebrovascular diseases such as cerebral arteriovenous malformation, arteriovenous fistula, or moyamoya disease.

Definition of variables and data collection

The patients' neurologic statuses were established based on retrospective analyses of their medical records. The severity of SAH was assessed with the Fisher Grade (FG) based on computed tomography (CT) imaging, and with the Hunt and Hess (H&H) Grade based on clinical presentation.

Patient-specific characteristics collected in the study are shown in Table 1. Heart comorbidities were defined as coronary heart disease, heart valve disease, arrhythmias, and heart dysfunction. Cerebral ischaemic comorbidities were defined as cerebral infarction, transient ischaemic attack, and cerebral vascular stenosis, coronary artery bypass grafting, and percutaneous transluminal coronary arthroplasty. In addition, we collected data on aspirin and statins use (excluding patients on dual antiplatelet agents or non-aspirin antiplatelet agents) at the time of diagnosis of the intracranial aneurysms.

The following morphometric measurements of the aneurysmal characteristics were taken: bifurcation aneurysms (yes/no), multiple IAs (yes/no), irregular shape (yes/no), and location (internal carotid artery rather than the posterior communicating artery/posterior communicating artery/anterior communicating artery/middle cerebral artery/posterior circulation). We also collected the following variables: the size of the aneurysm, the aspect ratio (AR; dome-to-neck ratio), the size ratio (SR), and the inflow angle (≥ 90 degrees/< 90 degrees).

Table 1. Basic characteristics of all patients and SIAs

	N (%)
No.	160
Female	83 (51.9)
Age < 50 (years)	69 (43.1)
Hypertension	81 (50.6)
Diabetes mellitus	12 (7.5)
Hypercholesterolemia	10 (6.3)
History of stroke	11 (6.9)
Previous SAH	7 (4.4)
Cardiovascular diseases	9 (5.6)
Smoking	54 (33.8)
Alcohol use	41 (25.6)
Aspirin use	20 (12.5)
Statins use	17 (10.6)
Inflow angle < 90 degrees	88 (55.0)
Irregular shapes	99 (69.7)
Aneurysm size (< 3 mm)	49 (30.6)
Multiple aneurysms	17 (10.6)
AR (mean ± SD)	1.34 ± 0.83
SR (mean ± SD)	1.70 ± 0.77
Location	
ICA	23 (14.4)
ACoA	58 (36.3)
PCoA	36 (22.5)
ACA	12 (7.5)
MCA	9 (5.6)
PC	22 (13.8)
Location of bifurcation	122 (73.6)
H&H grade	
0	3 (1.9)
1	81 (50.6)
2	50 (31.3)
3	19 (11.9)
4	6 (3.8)
5	1 (0.6)
FG	
1	4 (2.5)
2	79 (49.4)
3	51 (31.9)
4	26 (16.3)

SD — standard deviation; AR — aspect ratio; SR — size ratio; PCoM — internal carotid-posterior communicating artery; ACoA — anterior communicating artery; MCA — middle cerebral artery; ICA — internal carotid artery; PC — basilar tip and basilar-superior cerebellar artery AND vertebral artery–posterior inferior cerebellar artery and vertebrobasilar junction; ACA — anterior cerebral artery

Bifurcation aneurysms were defined as aneurysms located at the parent artery bifurcations (anterior communicating artery, internal carotid artery terminus, posterior communicating artery, middle cerebral artery bifurcation, and the apex of the

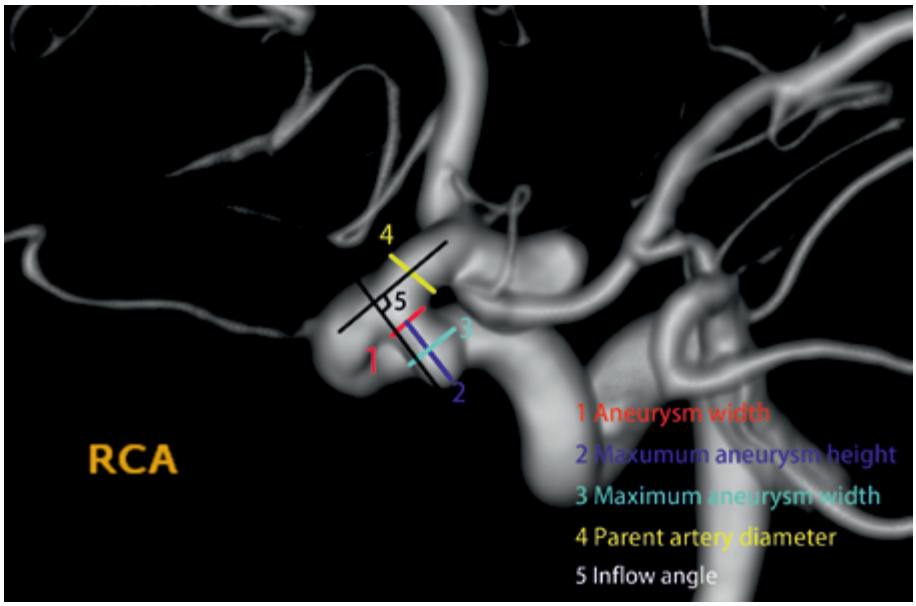

Figure 1. Aneurysm parameter definitions

basilar artery). Size ratio (SR) was defined as the maximum aneurysm height/average of the parent diameter. The aspect ratio (AR) was defined as the ratio of the maximum perpendicular height to the average neck diameter. Inflow angle was defined as the angle between the axis of flow in the parent vessel at the level of the aneurysm neck and the aneurysm's main axis from the centre of the neck to the tip of the dome (Fig. 1).

All morphological parameters were based on three-dimensional CTA/DSA imaging results and evaluated by two experienced neurosurgeons.

Statistical analysis

The data used in this study was analysed using SPSS software (SPSS 23.0, Chicago IL, USA). Data was analysed using frequencies (percentages) for categorical variables and mean ± SD for continuous variables. Data relating to categorical variables was analysed with Fisher's exact test or the Pearson chi-square test. Data relating to continuous variables was analysed using the Mann–Whitney U test or Student's *t*-test. Unconditional logistic regression analysis was used to calculate univariate and multivariate odds ratios (ORs) with 95% confidence intervals (CI). A P-value < 0.05 was regarded as statistically significant.

Results

Study population

A total of 160 patients (84 women and 76 men) with ruptured SIAs (< 5 mm) were retrospectively analysed in this study. Thirty-two patients were excluded for the following reasons: inability to identify the location of the ruptured aneurysm in multiple IAs (n = 17); dissecting, fusiform or traumatic aneurysm (n = 10); or aneurysms that were related to a cerebral arteriovenous malformation, arteriovenous fistula, or moyamoya disease (n = 5). Baseline characteristics of all patients and SIAs are shown in Table 1.

Univariate analyses

In univariate analysis, the following covariates met our previously determined level of significance and entered the forward stepwise selection for the unconditional logistic model: previous SAHs ($P < 0.006$), smoking ($P = 0.007$), alcohol use ($P = 0.048$), aspirin use ($P = 0.001$), inflow angle < 90 degrees ($P = 0.053$), aneurysm size (≥ 3 mm, < 5 mm) ($P = 0.102$), and a higher SR ($P = 0.001$) (Tab. 2).

Factors that were significantly associated with a higher FG (3–4) were smoking ($P = 0.019$), aspirin use ($P = 0.031$), inflow angle < 90 degrees ($P = 0.011$), and aneurysm size (≥ 3 mm, < 5 m) ($P = 0.039$) (Tab. 3).

Multivariate analyses

In the final adjusted multivariate analysis, the following covariates met our previously determined level of significance and entered the forward stepwise selection for the unconditional logistic model: previous SAH (OR, 12.245, 95% CI, 2.261–66.334, $P = 0.004$), aspirin use (OR, 4.677, 95% CI, 1.392–15.718, $P = 0.013$), alcohol use (OR, 3.392, 95% CI, 1.146–10.045, $P = 0.027$), inflow angle < 90 (OR, 3.881, 95% CI, 1.273–11.831, $P = 0.017$), and higher SR (OR, 6.611, 95% CI, 2.235–19.560, $P = 0.001$) were independent risk factors for a higher H&H grade in ruptured SIAs (Tab. 2).

In the final adjusted multivariate analysis, smoking (OR, 2.157, 95% CI, 1.061–4.384, $P = 0.034$), and inflow angle < 90 (OR, 2.603, 95% CI, 1.324–5.115, $P = 0.006$) were independent risk factors for a higher FG (3–4) (Tab. 3).

Table 2. Univariate analysis and multivariate analysis between H&H 1–2 group and H&H 3–5 group

Characteristic	H&H 1–2	H&H 3–5	Univariate analysis	Multivariate analysis	
			P	OR	P
Female	74 (55.2)	9 (34.6)	0.085		
Age < 50 (years)	60 (44.8)	14 (53.8)	0.520		
Hypertension	67 (50.4)	14 (53.8)	0.832		
Diabetes mellitus	10 (7.5)	2 (7.7)	1.000		
History of stroke	9 (6.8)	2 (7.7)	0.146		
Previous SAH	4 (3.0)	5 (19.2)	0.006	12.245 (2.261–66.334)	0.004
Cardiovascular diseases	7 (5.3)	1 (3.8)	1.000		
Smoking	39 (29.1)	15 (57.7)	0.007		
Alcohol use	30 (22.4)	11 (42.3)	0.048	3.392 (1.146–10.045)	0.027
Aspirin use	11 (8.2)	9 (34.5)	0.001	4.677 (1.392–15.718)	0.013
Statins use	12 (9.0)	5 (19.2)	0.133		
Inflow angle < 90 degrees	69 (51.5)	19 (73.1)	0.053	3.881 (1.273–11.831)	0.017
Irregular shapes	94 (70.7)	20 (76.9)	0.637		
Aneurysm size (≥ 3 mm, < 5 mm)	89 (66.4)	22 (84.6)	0.102		
Multiple aneurysms	15 (11.2)	2 (7.7)	1.000		
AR (mean ± SD)	1.37 ± 0.85	1.18 ± 0.70	0.287		
SR (mean ± SD)	1.69 ± 0.75	2.22 ± 0.78	0.001	6.611 (2.235–19.560)	0.001
Location					
ICA	20 (14.9)	3 (11.5)	0.696		
ACoA	47 (35.1)	11 (42.3)			
PCoA	30 (22.4)	6 (23.1)			
ACA	9 (6.7)	3 (11.5)			
MCA	9 (6.7)	0 (0)			
PC	19 (14.2)	3 (11.5)			
Bifurcation	101 (75.0)	21 (80.8)	0.800		

Discussion

In this study, the main finding was that inflow angle affected both the higher H&H grade (3–5) and the FG (3–4). In addition, aspirin use, previous SAH, alcohol use, and higher SR were independent risk factors for a higher H&H grade in ruptured SIAs. Smoking was an independent risk factor for a higher FG (3–4). Therefore, the clinical management of small (< 5 mm) unruptured IAs with these underlying factors should be more comprehensive and should be carried out more cautiously.

Inflammation plays a major role in the formation, progress, and rupture of IAs; several anti-inflammatory drugs have been tested for their potential to decrease IA formation and rupture [14, 16–19]. Aspirin has emerged as the most promising medical therapy for decreasing the incidence of aneurysmal subarachnoid haemorrhage by counteracting proinflammatory pathways and stabilising aneurysmal walls [17, 18]. Several population-based studies that have studied the association between antiplatelet therapy and subarachnoid haemorrhage (SAH) have had conflicting results. The International Study of Unruptured Intracranial Aneurysms (ISUIA) investigators reported that patients who used aspirin at least three times weekly had significantly lower risks of aneurysm rupture than those who never used aspirin, suggesting that frequent aspirin use may have a protective effect on blood vessels [20]. Along similar lines, Garcia Rodriguez et al., using data from the health improvement network, reported a lower risk of SAH with long-term aspirin intake [19]. In contrast, the use of low-dose aspirin has been associated with an increased risk of SAH in the first month after starting treatment [21]. A recent meta-analysis of seven studies suggests an increased risk of aSAH among short-term (< 3 months) aspirin users [15]. The exact mechanism by which aspirin may exert its effects on aneurysm prognosis and rupture is unclear. Recent studies have shown that aspirin (e.g. acetylsalicylic acid) may stabilise aneurysm walls and counteract proinflammatory pathways [14, 22]. In addition, walls of ruptured IAs have higher levels of cyclooxygenase-2 and microsomal prostaglandin E2 synthase 1, both of which are inhibited by aspirin [22]. However, there is little evidence to identify the effect of aspirin use on clinical

Table 3. Univariate analysis and multivariate analysis between FRS 1–2 group and FRS 3–4 group

Characteristic	FRS 1–2	FRS 3–4	Univariate analysis	Multivariate analysis	
			P	OR	P
Female	47 (56.0)	36 (47.4)	0.342		
Age < 50 (years)	44 (52.4)	42 (55.3)	0.752		
Hypertension	39 (47.0)	42 (55.3)	0.832		
Diabetes mellitus	6 (7.1)	6 (8.0)	1.000		
History of stroke	4 (4.8)	7 (9.3)	0.351		
Previous SAH	3 (3.6)	6 (7.9)	0.312		
Cardiovascular diseases	3 (3.6)	5 (6.7)	0.477		
Smoking	21 (25.0)	33 (43.4)	0.019	2.157 (1.061–4.384)	0.034
Alcohol use	18 (21.4)	23 (30.3)	0.211		
Aspirin use	6 (7.1)	14 (18.4)	0.031`		
Statins use	6 (7.1)	11 (14.5)	0.133		
Inflow angle < 90 degrees	38 (45.2)	50 (65.8)	0.011	2.603 (1.324–5.115)	0.006
Irregular shapes	62 (74.7)	52 (68.4)	0.481		
Aneurysm size (≥ 3 mm < 5 mm)	52 (61.9)	59 (77.6)	0.039		
Multiple aneurysms	9 (10.7)	8 (10.5)	1.000		
AR (mean ± SD)	1.37 ± 0.90	1.31 ± 0.74	0.669		
SR (mean ± SD)	1.74 ± 0.87	1.81 ± 0.67	0.585		
Location					
ICA	16 (19.0)	7 (9.2)	0.696		
ACoA	30 (35.7)	28 (36.8)			
PCoA	15 (17.9)	21 (27.6)			
ACA	4 (4.8)	10 (10.5)			
MCA	7 (8.3)	2 (2.6)			
PC	12 (14.3)	10 (13.2)			
Bifurcation	63 (75.9)	59 (77.6)	0.852		

and radiographic grades of SAH caused by SIAs. In our study, aspirin use was significantly associated with a higher H&H grade in ruptured SIAs, whereas statin use was probably not associated with a higher H&H grade or FG.

Ours is the first study in which aspirin has been significantly associated with higher H&H grades; further studies are needed to determine the safety of aspirin as an emerging potential medical therapy for the prevention of IA rupture.

In the study, we found that inflow angle affected both the higher H&H grade (3–5) and the FG (3–4). Baharoglu et al. evaluated maximal dimension, height–width ratio, and dome–neck aspect ratio sidewall-type aneurysms with respect to the rupture status in a cohort of 116 aneurysms in 102 patients. They found that inflow angle is a significant discriminate of rupture status in aneurysms and is associated with significantly greater peak velocities and kinetic energy transmission to the dome [23]. Tykocki et al. found that inflow angle proved to be a relevant predictor in estimating the aneurysm risk rupture of the posterior cerebral circulation [24]. Similarly, Lv et al. also reported that inflow angle was significantly different between ruptured and unruptured small posterior communicating artery aneurysms [25]. The most important finding of this study was that inflow angle was the only independent risk factor for both H&H grade and FG. Moreover, for simpler clinical measurements, we divided the inflow angle into ≥ 90 degrees / < 90 degrees. In the present study, it was observed that 71.3% of patients with poorer H&H (3–5) had an inflow angle < 90 degrees, and 65.8% of patients with poorer FG (3–4) had an inflow angle < 90 degrees. One possible explanation is that a greater inflow angle leads to an increase of the wall shear stress (WSS), spatial gradient, and results in a more direct flow into the aneurysm dome. These altered blood flow parameters in the aneurysm lumen may increase the risk of aneurysm rupture, and then if bleeding is not quickly stopped after the aneurysm rupture there would be a resultant increase in bleeding volume, and a poorer grade of H&H and FG [26–28].

The importance of the SR has been emphasised in many studies. As a promising new morphological parameter, the SR was first proposed by Dhar et al, when they reported that SR was associated with the rupture of IAs [7]. Several studies have shown a significant relationship between SR and the

risk of rupture of small aneurysms. A study by Kashiwazaki in Japan revealed that SR might predict the risk of rupture in small unruptured IAs [5]. The study of Feng et al. also found that small IAs with larger SRs was associated with a greater rupture risk (OR, 2.766) [29]. However, there have been few studies on the possible mechanisms by which SR increases the risk of rupture. Markus reported that increasing SR aneurysm morphology presented multiple vortices and complex flow patterns and aneurysm luminal area was exposed to low wall shear stress increased with higher SR [30]. Complex flow, multiple vortices, and low aneurysmal wall shear stress have been associated with ruptured IAs in previous studies. These changes may lead to a higher risk of aneurysm rupture. In the present study, a higher SR was an independent risk factor for a higher H&H grade (3–5) in ruptured SIAs (Tab. 2). For two aneurysms of the same size, a high SR indicates a small-sized parent artery. However, the threshold value of SR for predicting aneurysm rupture is unknown, although several previous studies have reported a higher SR value being related to the rupture status of IAs. We found that aneurysms located distally in the anterior cerebral artery and M2/3 of the middle cerebral artery were consistently associated with a higher SR, and that ruptured SIAs at these locations were associated with greater risks of a higher H&H grade. However, a high SR was not significantly associated with a high FG (3–4). A possible reason for this finding is that the diameter of the distal vessel is small or the space around the vessel is small, so the amount of bleeding is small; therefore, the CT image shows a low FG.

AR was first proposed by Ujiie et al. and was defined as aneurysm depth to aneurysm neck width. They found that AR in 88% of ruptured aneurysms was higher than 1.6, while 56% of unruptured aneurysms had an AR lower than 1.6 [31]. A high AR was statistically more likely to have a greater low wall shear stress (WSS) area ratio that causes the dysfunction of the endothelium, which is consistent with the low flow theory [32]. The disruption and dysfunction of endothelial cells caused by non-physiological WSS is an important step in IA formation and rupture [33]. Therefore, a higher AR means a smaller neck and slower intra-aneurysmal blood flow, which reflects a higher risk of rupture. However, in our study, AR was not significantly associated with a high FG or a higher Hunt and Hess scale grade.

Female gender, history of SAH, and cigarette smoking have all been identified as independent risk factors for aneurysm rupture in previous studies [34–36]. In our study, previous SAH was significantly associated with a high Hunt and Hess scale grade, and smoking was significantly associated with a high FG. However, previous SAH was not significantly associated with a high FG, and smoking was not significantly associated with a high Hunt and Hess scale grade. It seems that patients with a history of SAH may have a poor neurological status and do not correlate to the severity of SAH on CT imaging. In this study, alcohol use and aneurysm size (≥ 3 mm, < 5 m) also had inconsistent performances in the analysis of risk factors for the Hunt and Hess scale and the FG. In order to explore the reasons for this inconsistent performance, we analysed the Spearman's test of correlation between the FG and the Hunt and Hess scale. The results showed that there was a significant correlation between the Fisher grading scale and the Hunt and Hess scale ($P < 0.001$).

Strengths and limitations

The strengths of our study include the rigorous measurement of parameters by more than two experienced neurologists, therefore ensuring the representativeness and repeatability of the data. Besides, this is the first retrospective and systematic analysis of the risk factors for neurologic status and radiologic extent of subarachnoid haemorrhage (SAH) in small ruptured aneurysms (< 5 mm). This is also the first study in which aspirin use has been significantly associated with a higher H&H grade in ruptured SIAs.

The data generated from this study provides some valuable information that may facilitate the evaluation of the safety of aspirin as an emerging potential medical therapy for preventing IA rupture. However, there were also several limitations to this study.

This study was retrospective in design and all patients were enrolled from a single centre, meaning there was an unavoidable choice bias. Secondly, the Hunt and Hess scale has been reported to have a poor interobserver agreement [36], so the World Federation of Neurosurgical Societies (WFNS) scale was chosen in some studies because of its predictability regarding values. Its application in the clinical environment is very common and convenient [37]. Finally, this study did not explore the effects of the Fisher grading scale and the Hunt and Hess scale on the outcome of ruptured SIAs patients; we will explore this separately in a future research paper.

Conclusions

In this study, the main finding was that two easily measurable morphological parameters, inflow angle and higher SR, were independent risk factors for the severity of SAH in SRAs. The clinical management of small aneurysms with these factors should be more cautious and comprehensive. Our findings also suggested that aspirin use was significantly associated with a higher H&H grade in ruptured SIAs. To ascertain whether aspirin should be instituted as a prophylactic measure in all patients with unruptured aneurysms requires a randomised controlled trial.

Conflict of interest: *None declared.*
Data availability statement: *All relevant data is within the paper.*
Ethics: *The study protocol was approved by the institutional review board at our hospital. All patients gave written informed*

consent to participate, and the privacy of patients was strictly protected.

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RESEARCH PAPER

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2019, Volume 53, no. 4, pages: 304–310
DOI: 10.5603/PJNNS.a2019.0035

ISSN 0028–3843

Altered functional brain imaging in migraine patients: BOLD preliminary study in migraine with and without aura

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ABSTRACT

Design. Migraine is regarded as a complex brain dysfunction of sensory and modulatory networks with the secondary sensitisation of the trigeminal system as well as the affected brain area's activities. The particular role of the hippocampus and the brainstem in the first phase of the attack, the disrupted cognitive network, and the activation of the limbic and visual systems, are the main discoveries in the field of migraine imaging that have been achieved using functional techniques. Thus advanced neuroimaging has been widely employed to study the pathogenesis of migraine.

Objective. The evaluation of fMRI BOLD images of migraine patients with or without aura, with particular attention to the interictal phase.

Material and methods. The aim of this study was to compare brain activity during visual stimuli by fMRI BOLD in the interictal phase (black and white checkerboard tests, static or flickering) of 16 migraine patients, eight with aura and eight without.

Results. We demonstrated differences in the right part of the brainstem, the left part of the cerebellum, and in the right middle temporal gyrus. However, the bilateral brain activation in the occipital and frontal lobe remained similar.

Conclusions. Results of our preliminary study suggest that migraine with aura and migraine without aura might be separate disorders, and this requires further investigation.

Key words: migraine, fMRI, BOLD MRI, trigeminovascular system

(*Neurol Neurochir Pol 2019; 53 (4): 304–310*)

Study of the interictal phase of migraine using BOLD fMRI neuroimaging technique

The pathogenesis of migraine still remains elusive. The mechanism of a migraine attack includes pathological vasomotor regulation associated with neuronal processes and abnormal cortical neuronal activity [1]. Reduction of the regional cerebral blood flow (rCBF) occurs during the migraine aura in the occipital cortex, as reported by a historical study by Olesen at al. [2]. Advancing wavefront propagates rostrally and centrifugally [1, 3–6] and this is associated with the distribution of cortical inhibition of neuronal activity known as cortical spreading depression (CSD) [7], a term coined by Leao et al. [8]. Studies of vascular changes sampling the parenchymal compartment (PET, fMRI, SPECT and scintigraphy), distinct from larger vessels (TSD), have demonstrated a different vascular response [9]. Single photon emission computerised tomography (SPECT) studies have described a cerebral blood flow reduction during visual aura, initially in the occipital cortex, and an increase of the blood flow during the pain phase in 50% of migraine patients [10, 11]. PET

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Table 1. Demographic characteristics of the study population

Patients	Sex M/F	Mean age+SD [years]	Mean attacks of migraine frequency
M n = 16	3/13	38 +/– 9	1 per 1 month
MwA n = 8	3/5	44 +/– 7.5	1 per 3 weeks
MWA n = 8	0/8	33 +/– 7	1 per 3 months

M — all patients with migraine; MwA — patients with migraine without aura; MWA — patients with migraine with aura

studies have reported minute, but significant, blood flow reduction in the occipital region contralateral to visual aura with normalisation of during pain phase. FMRI studies have demonstrated the presence of certain processes that still require elucidation in the field of basic research [12]. Nevertheless, studies based on blood oxygenation level-dependent MRI (BOLD-MRI) indicate the same course of events in both phases [13–16]. Thus, the BOLD-MRI technique has become one of the most widely used methods for measuring a migraineur's brain abnormalities more accurately, due to a larger resolution, the temporal (minor remark) and the spatial image of the brain's activity and its connectivity. BOLD neuroimaging may be the most promising methodological advance in functional migraine studies. However, our preliminary data requires further investigation.

Materials and methods

Participants were recruited from 16 migraine patients who had received treatment in the outpatient Headache Clinic: eight with aura (MWA), all females with a mean age of 33 + 7 years) and eight without aura (MwA), five females and three males with a mean age of 44 + 7.5 years. The mean age of the entire group was 38 + 9 years and the duration of the disease was between two and 35 years. All patients eligible for inclusion in the study were diagnosed with MWA or MwA using the International Headache Society (IHS) criteria (Tab. 1), based on the most recent 3rd edition from 2018 [19] and were examined by an experienced clinician. The frequency of migraine attacks ranged from one per week to one per annum (mean frequency: one per month).

The study group consisted of patients who visited the clinic during a spontaneous migraine attack. MWA patients with aura arrived at the clinic usually earlier than MwA patients without aura. Patients had to be chronologically chosen due to the limited number of participants (non-matched age), thus this results study has to be interpreted as preliminary.

We obtained the approval of the ethical committee of Warsaw Medical University as required for this study and modified in accordance with the Declaration of Helsinki. A written consent was signed by all participants.

Image acquisition

Routine MRI scans were obtained using standard equipment (3 T Siemens Magnetom Trio Tim MR) and a standard protocol. fMRI data collected between attacks of migraine were acquired by an experienced physician with no knowledge of the diagnosis.

Image analysis

The fMRI study included standard anatomical 3D T1-weighted images of the whole-brain analyses (3D MP-RAGE sequence, TR = 1,900 ms, TE = 2.26 ms, 0.9 × 0.9 × 0.9 mm voxels), 172 slices in total (TA = 6 min 32 s), and gradient of Echo-Planar Imaging (EPI) sequences [TR = 3,000 ms, TE = 30 ms, flip angle = 90°, FOV 192 × 192 mm Matrix size was 96 × 96, each volume consisted of 47 axial slices, 3 mm thick (no gap, 2 × 2 × 3 mm voxel), pixel bandwidth = 1,532Hz/pix, iPAT = 2] obtained using 12-channel matrix head coil and MR compatible goggles (Nordic NeuroLab Visual system) in the Bioimaging Research Centre of the Institute of Physiology and Pathology of Hearing in Warsaw, Poland. The images were analysed using Statistical Parametric Mapping (SPM12b, http://www.fil.ion.ucl.ac.uk/spm/software/spm12) and adjusted for motion correction and spatial normalisation (a least squares approach and a six parameter spatially normalized, reference to the first scan) to the standard Montreal Neurological Institute (MNI) template in SPM 12b (resampling voxel size = 2 × 2 × 2 mm). Static and flickering checkerboard test results were individually preprocessed (first level analysis). Cortical activation was separately analysed and compared for both groups using the two sample t test.

Results

There were no demographic differences in terms of age and gender between the MwA and MWA patients. Significant ($p < 0.001$, uncorrected) similar bilateral activations were located predominantly in the occipital lobe, in the cuneus and the lingual gyrus as well as in various regions of the frontal cortex (presented in Figs. 1 and 2 and in Tabs. 2 and 3). Increased fMRI activity in the right brainstem, the left part of the cerebellum and in the right middle temporal gyrus (Fig. 3, Tab. 4) was found in the MWA group. There were no statistically significant differences in those regions during the flickering checkerboard

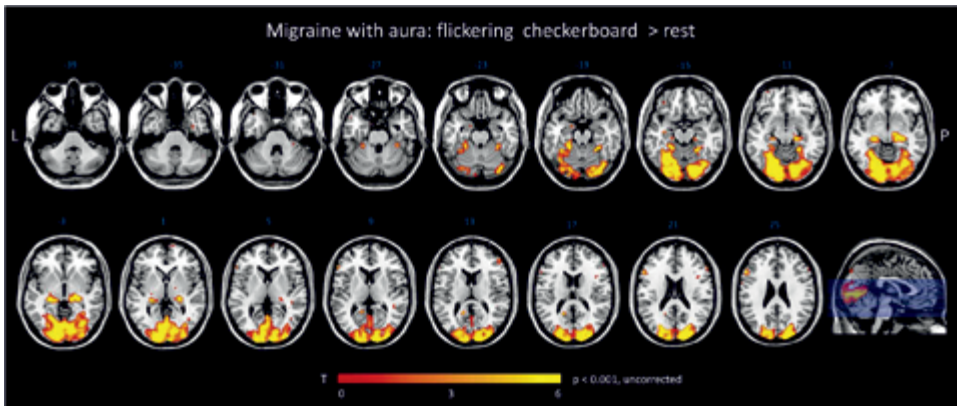

Figure 1. Activations in response to a flickering checkerboard in migraine with aura

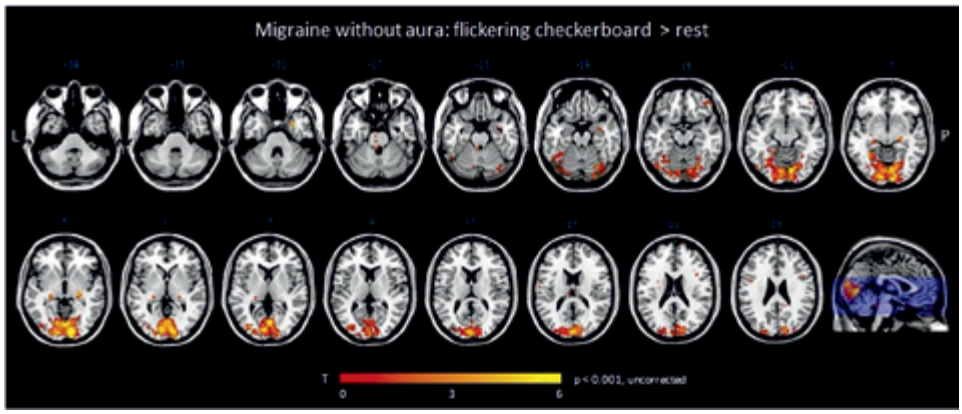

Figure 2. Activations in response to a flickering checkerboard in migraine without aura

Table 2. Brain areas (MNI coordinates, number of voxels and z scores, p < 0.001, uncorrected) activated in the flickering checkerboard block in migraine with aura

Region	Side	Brodmann's area	MNI coordinates (x, y, z)	No. of voxels	Z statistics
Occipital lobe	L + R	18, 19	-20 -62 -2	8,333	5.15
Brainstem	R	-	-24 -26 -4	320	5.36
Hippocampus	L	-	-26 -30 -2	172	4.32
Cerebellum	R	-	-24 -46 -18	127	4.54
Cerebellum	L	-	-22 -40 -18	150	4.14
Precuneus	L	7	-4 -84 -46	64	4.34
Middle frontal gyrus	L	45	-54 -22 -24	48	3.69

L — left; R — right

block test (Figs. 4–5, Tabs. 5–6). At the same time, increased bilateral activity was observed in the brainstem, in the right part of the cerebellum, and in the left medial frontal gyrus of the MwA patients (Fig. 6, Tab. 7).

Discussion

The preliminary data indicates a substantial difference in BOLD-fMRI response patterns between MWA and MwA patients.

In the MWA group, increased response in the right part of the brainstem, the left hemisphere of the cerebellum, and the right middle temporal gyrus corresponds (minor remark) with hyperresponsiveness within the primary visual cortex and the lateral geniculate nuclei. Greater activation of the primary visual cortex of migraneurs and differences in the activation of lateral geniculate nuclei between MWA and MwA patients were also reported in a recent prospective case-control study [20, 21]. We also found a difference between the MWA and

Table 3. Brain areas (MNI coordinates, number of voxels and z scores) activated in the flickering checkerboard block in migraine without aura ($p < 0.001$, uncorrected)

Region	Side	Brodmann's area	MNI coordinates (x, y, z)	No. of voxels	Z statistics
Occipital lobe	L + R	17,18	-12 -92 -6	1,247	3.87
Lingual gyrus					
Cuneus					
Cuneus	R	18	14 -86 -16	53	3.45
Lingual gyrus	R	18	26 -72 -14	24	3.41
Superior frontal gyrus	R	9	-18 -48 -48	25	4.71

L — left; R — right

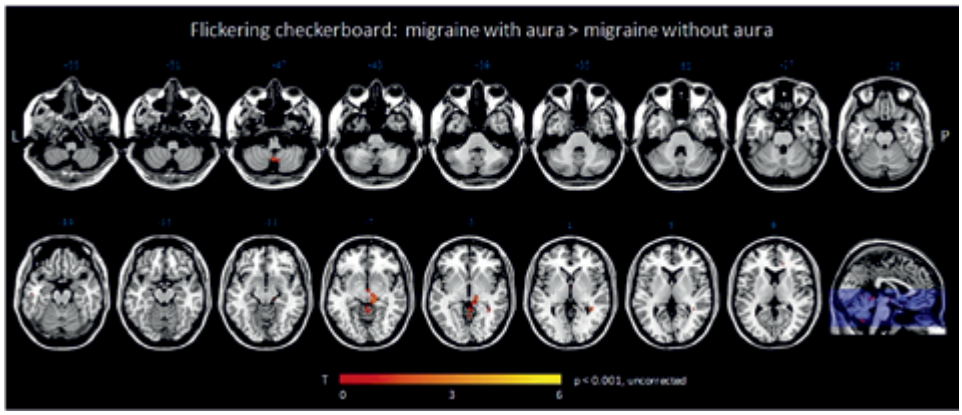

Figure 3. Activations elicited by a flickering checkerboard in contrast: migraine with aura *vs.* migraine without aura patients

Table 4. Brain areas (MNI coordinates, number of voxels and z scores) involved in a flickering checkerboard perception for contrast: migraine with aura *vs.* without aura patients ($p < 0.001$, uncorrected)

Region	Side	MNI coordinates (x, y, z)	No. of voxels	z statistics
Brainstem	R	10 -20 -6	172	4.03
Cerebellum	L	-2 -62 -46	37	3.77
Middle temporal gyrus	R	38 -44 2	29	3.66

L — left; R — right

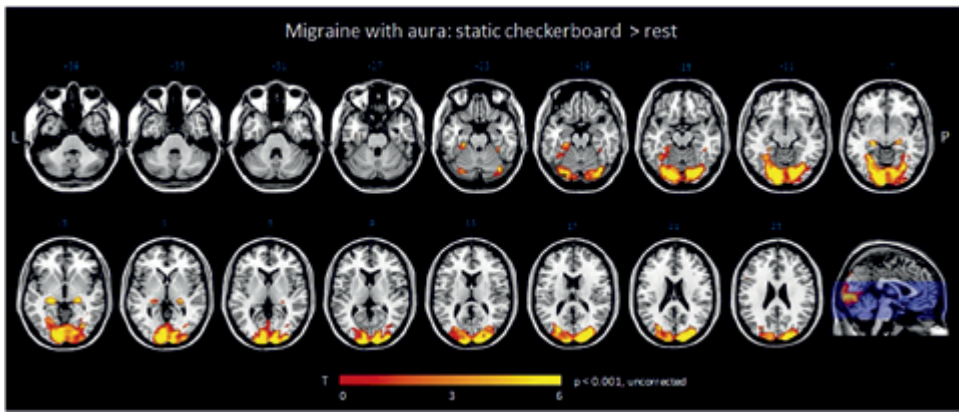

Figure 4. Activations in response to a static checkerboard in migraine with aura

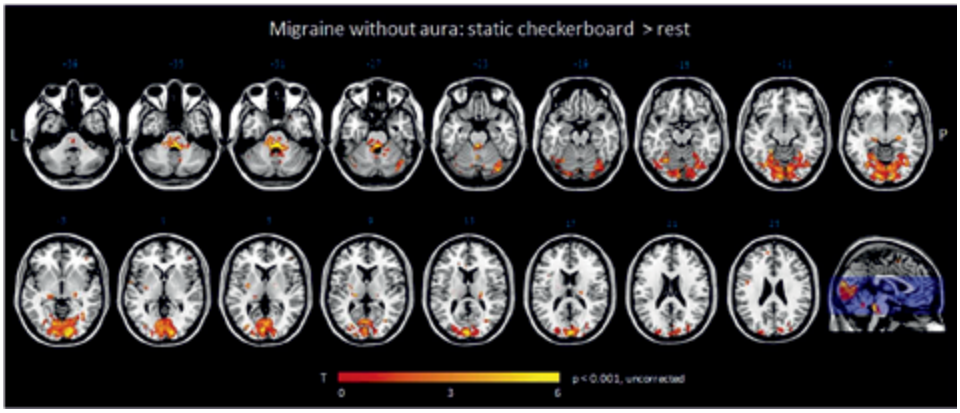

Figure 5. Activations in response to a static checkerboard in migraine without aura

Table 5. Brain areas (MNI coordinates, number of voxels and z scores) activated in the static checkerboard block in migraine with aura (p < 0.001, uncorrected)

Region	Side	Brodmann's area	MNI coordinates (x, y, z)	No. of voxels	Z statistics
Occipital lobe	L + R	18, 19	-8 -92 0	5,626	4.99
Lingual gyrus					
Cuneus					
Cerebellum					
Hippocampus	L	-	-26 -28 -4	124	6.19
Parahippocampa gyrus	L	36	-26 -28 -22	39	4.17
Thalamus	R		24 -26 -2	86	4.30

L — left; R — right

Table 6. Brain areas (MNI coordinates, number of voxels and z scores) activated in the static checkerboard block in migraine without aura (p < 0.001, uncorrected)

Region	Side	Brodmann's area	MNI coordinates (x, y, z)	No. of voxels	z statistics
Occipital lobe	L	17,18	-30 -62 -18	752	3.98
Lingual gyrus					
Cuneus					
Occipital lobe	R	17	8 -96 -4	230	3.82
Lingual gyrus					
Brainstem	L + R	-	4 -36 -30	311	4.66
Cerebellum	R		34 -80 -26	76	3.75
Inferior occipital gyrus	R		40 -68 -8	45	3.62

L — left; R — right

MwA groups that could possibly imply an association between these two variables, the presence of aura and its cortical hyperresponsiveness. This gives potential for further investigation.

According to Martin et al. [15], the brains of migraineurs demonstrate hyperexcitability of the visual cortex during interictal periods, with more spacious areas of photoresponse due to the paired mechanism: constitutional (defensive) and acquired (sensitisation). Moreover, BOLD alterations during the onset of a migraine attack with visual aura coincided with the onset of the aura and progressed throughout the occipital cortex at the velocity of 3–5 mm per minute and declined after the initial increase [22]. The BOLD signal activation in the brainstem structures, specifically in the red nucleus and substantia nigra, indicates that these structures are also involved in the migraine attack in MWA patients [23, 24]. An altered activation pattern in the migraine phase has also been demonstrated in several subcortical and cortical regions [25].

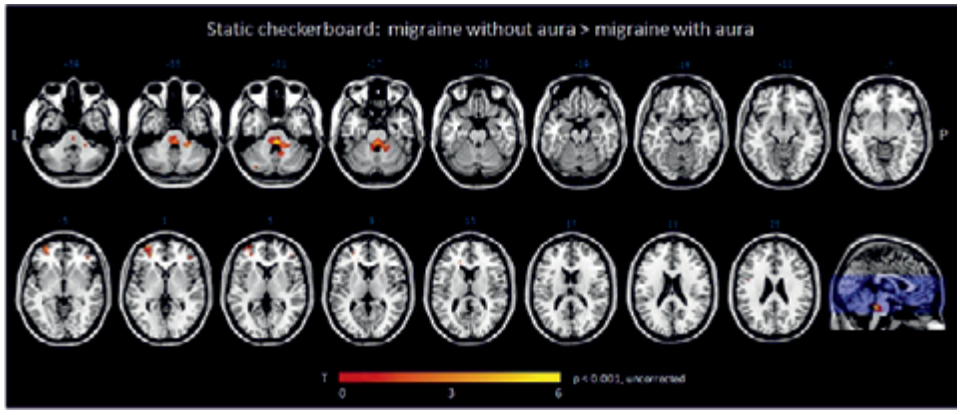

Figure 6. Activations elicited by a static checkerboard in contrast: migraine without aura *vs.* migraine with aura patients

Table 7. Brain areas (MNI coordinates, number of voxels and z scores) involved in a static checkerboard perception for contrast: migraine with aura vs. without aura patients ($p < 0.001$, uncorrected)

Region	Side	Brodmann's area	MNI coordinates (x, y, z)	No. of voxels	z statistics
Brainstem *Pons*	L + R		-2 -36 -28	431	4.23
Cerebellum	R	-	10 -52 -30	41	3.73
Medial frontal gyrus	L	10	-32 58 -2	118	3.93

L — left; R — right

In our study, we found brainstem activation in patients with MWA during the interictal phase, whereas an increased activation was found in part of the cerebellum and in the left medial frontal gyrus of MwA patients.

It is unclear whether the frequency of migraine attacks affects activation of particular brain regions and if so, it is rather increased frequency and its activity during migraine's attacks. The result of our study indicates a different pathomechanism of the attack in MwA patients compared to MWA patients. The distinct response patterns during brainstem activation observed in our study suggest two separate types of migraine attack. Unfortunately, an insufficient analysis of macro- and microstructural changes, both cortical and subcortical, the absence of a control group, unmatched age, gender and the frequency of migraine attacks in our study are limitations of our study. However, age and gender play insignificant roles in brain activation during attacks. Therefore our results have to be interpreted as preliminary. Further investigation is required for a better understanding of the pathomechanism during a migraine attack.

Nevertheless, the combination of functional and structural techniques to acquire and analyse function and organisation of the CNS in basic migraine studies could provide a more effective approach to propose a unique model of migraine events [12, 26].

Insight into the pain circuits altered in migraine could potentially contribute to the development of a new rs-fMRI-based, noninvasive migraine indicator. More accurate classification, and analysis of long term migraneurs, could potentially indicate that the duration of the disease plays a crucial role in the "reorganization of brain circuitry" [27, 28].

Compliance with ethical standards

There were no conflicts of interest and commercial relationships including grants, honoraria, speaker's lists, significant ownership, and/or support from pharmaceutical or other companies, during our study.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee.

Informed consent was obtained from all individual participants included in the study.

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SHORT COMMUNICATION

Neurologia i Neurochirurgia Polska
Polish Journal of Neurology and Neurosurgery
2019, Volume 53, no. 4, pages: 311–314
DOI: 10.5603/PJNNS.a2019.0031

ISSN 0028–3843

The symptoms asymmetry of drug-induced parkinsonism is not related to nigrostriatal cell degeneration: a SPECT-DaTSCAN study

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ABSTRACT

Aim. Drug-induced parkinsonism (DIP) is the most common form of parkinsonism after Parkinson's disease (PD) itself. It has been widely believed that DIP is characterised by symmetry of symptoms. Studies of patients with DIP in whom PD had been ruled out by SPECT-DaTSCAN have shown that symptom asymmetry is a common element of DIP clinical presentation. The aim of our study was to determine whether the asymmetry of symptoms in DIP is related to any abnormality within the presynaptic part of the nigrostriatal dopaminergic system.

Materials and methods. Eleven patients with the diagnosis of DIP and asymmetric symptoms were studied. Their individual SPECT-DaTSCANs were normal. Indices calculated for the whole group of radiotracer uptake in the whole striatum, putamen and caudate contralateral to more severe DIP symptoms were compared to values obtained in the opposite hemisphere.

Results. We did not find significant differences in radiotracer uptake in structures contralateral to more severe clinical symptoms when compared to the homolateral hemisphere.

Conclusions. Our results have not confirmed the presence of a presynaptic nigrostriatal deficit which could be related to asymmetry of DIP. The factors responsible for the asymmetry of DIP symptoms should be sought in the postsynaptic part of the nigrostriatal dopaminergic system.

Key words: drug-induced parkinsonism, asymmetry of symptoms, presynaptic nigrostriatal deficit, SPECT-DaTSCAN (*Neurol Neurochir Pol 2019; 53 (4): 311–314*)

Introduction

Idiopathic Parkinson's disease (PD) and drug-induced parkinsonism (DIP) are the two most common forms of parkinsonism [1, 2]. In PD, motor symptoms are caused by neurodegeneration of presynaptic neurons of the nigrostriatal dopaminergic system, while DIP is related to the post-synaptic dopaminergic receptor blockade within the striatum. The differential diagnosis of PD and DIP can be a challenge, especially in older people, because increasing age is a recognised as a risk for both these conditions [1, 2]. It is very important to identify persons with PD in a group of patients taking dopamine receptor blocking agents (DRBA) and in whom parkinsonism has developed because the treatment and prognosis are completely different. Therefore, attention has been paid to differences in the clinical presentations of PD and DIP, which could be useful in differential diagnosis. It has generally been assumed that DIP is characterised by symmetry of symptoms, the absence of rest tremor, and the co-occurrence of bucco-linguo-masticatory dyskinesia and akathisia [1–3].

^{123}I-Ioflupane (DaTSCAN®, GE Healthcare) is a dopamine transporter (DAT) radioligand for single-photon emission

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tomography (SPECT). A SPECT-DaTSCAN is used as a marker of integrity of the presynaptic part of the nigrostriatal dopaminergic system [4, 5]. Studies of patients diagnosed with DIP, in whom SPECT-DaTSCAN had excluded the coexistence of PD, have shown that the symptomatology of these two conditions shows many similarities and that asymmetry of symptoms is common in DIP [6–9]. The aim of our study was to determine whether the asymmetry of symptoms in DIP is related to any abnormality within the presynaptic part of the nigrostriatal dopaminergic system.

Material and methods

Patients

Our study initially enrolled 13 consecutive patients who underwent SPECT-DaTSCAN for the differential diagnosis between DIP and PD. In two of these subjects the imaging revealed abnormalities consistent with neurodegenerative parkinsonism. The remaining 11 patients (eight females and three males, mean age 64 years) were included into the study. All of them presented at least two of the three main (bradykinesia, rigidity, rest tremor) parkinsonian symptoms, and these symptoms were either asymmetric or unilateral. Subjects with signs suggesting an atypical parkinsonian syndrome, or other neurological conditions, were not included.

The duration of exposure to drugs implicated in DIP ranged from 2-14 years, while parkinsonian symptoms had lasted from 1-84 (mean 18.6) months. The onset of parkinsonism was subacute or chronic. The time from the start of psychiatric treatment to the development of parkinsonian symptoms ranged from 3-24 months. Patients were treated with different drugs and some of them received two or more drugs at the same time. The drugs most commonly used in this group at the time of the evaluation of parkinsonism were risperidone, aripiprazole, olanzapine and perazine.

SPECT-DaTSCAN

SPECT/CT acquisitions were performed with double-head hybrid gamma-camera Infinia Hawkeye GE 4 h after i.v. administration of 5 mCi of 123I-Ioflupane. Prior to radiotracer injection, patients received orally potassium iodine to block thyroid uptake of free radioactive iodide. Data was acquired with the use of low energy high resolution (LEHR) collimators in dual energy window: 159 keV ± 10% (scatter: 130 keV ± 10%), in 128 × 128 matrix. Using a step-and-shoot method, 120 projections lasting 45 s each were registered with the use of zoom equal 1.5. Images reoriented to the orbitomeatal plane were reconstructed with the OSEM method (2 iter., 10 sub., postfilter: Butterworth 0.50/10) with scatter correction and attenuation correction (Chang method).

The analysed SPECT-DaTSCAN variables were 123I-Ioflupane uptake ratios in the entire striatum, putamen and caudate in both hemispheres. SPECT-DaTSCAN images were analysed semi-quantitatively by a nuclear medicine physician expert in neuroimaging. The quantitative assessment of DaTSCAN-SPECT images was made using DaTQUANT delivered by GE Healthcare.

In order to ascertain the relationship between the asymmetry of clinical symptoms of DIP and the result of the SPECT-DaTSCAN, the indices of radiotracer uptake in the whole striatum, putamen and caudate contralateral to more severe symptoms were compared to the respective values obtained in the opposite hemispheres. Moreover, putamen/caudate ratios for both sides were calculated.

The distribution of indices of tracer uptake obtained on both sides in each structure were compared by means of the Wilcoxon test for paired samples.

Results

The individual SPECT-DaTSCAN results of all patients were considered to be normal. Indices of 123I-Ioflupane uptake in the whole striatum, putamen and caudate for both sides, as well as the values of the putamen/caudate ratio, are presented in Table 1.

Discussion

DIP is the most common form of parkinsonism after PD [1, 2]. The diagnosis of DIP is relatively easy provided that there is an unequivocal temporal relationship between the DRBA introduction and the occurrence of parkinsonism, and even more so if discontinuation of offending drug leads to the resolution of DIP symptoms.

However, DIP can develop gradually after prolonged exposure to neuroleptic and, moreover, DIP can persist despite discontinuation of the drug. In such cases, it may be suspected that the patient being treated with DRBA develops PD, and the neuroleptic only contributes to its earlier manifestation. This is referred to as 'unmasking of PD by DRBA' [8, 10].

Both for the psychiatrist and for the neurologist it is crucial to decide whether the patient has pure DIP or Parkinson's disease, the course of which could have been modified by the DRBA administration. The differential diagnosis between PD and DIP can be challenging, especially because both forms of pathology can co-exist. This applies primarily to the elderly population.

In the past, this differentiation was based on clinical symptoms. It was widely believed that DIP is characterised by symmetry of symptoms, lack of tremor or the presence of postural tremor, the occurrence of bucco-lingual-masticatory dyskinesia, and akathisia [1–3].

In clinical practice, a SPECT-DaTSCAN is performed to differentiate between neurodegenerative parkinsonisms (e.g. PD) on the one hand, and on the other hand parkinsonian syndromes without presynaptic involvement (e.g. DIP) of the nigrostriatal dopaminergic system [9, 11, 12]. Studies of patients with DIP in whom the co-existence of PD has been

Table 1. Results of DaTSCAN imaging. Indices of radiotracer uptake (normalised to nonspecific uptake in occipital cortex) the whole striatum, putamen and caudate are presented. Moreover, putamen/caudate ratios for both sides were calculated

Structure	Side	Indices of radiotracer uptake			p*
		Mean ± SD	Minimum-maximum	Median	
Striatum	Contralateral	2.54 ± 0.29	1.85–2.94	2.61	0.59
	Ipsilateral	2.57 ± 0.32	1.79–2.97	2.64	
Putamen	Contralateral	2.41 ± 0.31	1.74–2.80	2.47	0.51
	Ipsilateral	2.44 ± 0.32	1.64–2.82	2.51	
Caudate	Contralateral	2.83 ± 0.32	2.12–3.25	2.91	0.88
	Ipsilateral	2.86 ± 0.34	2.09–3.26	2.94	
Putamen/caudate	Contralateral	0.89 ± 0.07	0.81–1.02	0.88	0.72
	Ipsilateral	0.89 ± 0.03	0.86–0.98	0.88	

Contralateral — side opposite to the side where the symptoms of DIP were more severe; Ipsilateral — side where the symptoms of DIP were more severe; *Wilcoxon test for paired samples

ruled out by SPECT-DaTSCAN have shown that symptom asymmetry is a not uncommon element of DIP clinical presentation.

Some authors have reported asymmetry of symptoms to be less common than symmetry in DIP [6, 7], while others have not found significant differences in asymmetry of tremor, bradykinesia and stiffness between patients with a normal and an abnormal SPECT-DaTSCAN [8]. A recently published study [9] revealed asymmetry of symptoms in 88% of subjects with a diagnosis of DIP and a normal SPECT-DaTSCAN. The cause of the asymmetry of DIP symptoms has never been studied or discussed to date.

The term 'unmasked PD' has not been clarified so far. It was usually used for cases when the symptoms of parkinsonian syndrome appeared after neuroleptic administration and where the SPECT-DaTSCAN showed asymmetric deficit of the presynaptic part of the nigrostriatal system.

Prospective studies carried out in patients with REM Sleep Behaviour Disorder (RBD), which is a pre-motor manifestation of PD and other synucleinopathies, have shown that nigrostriatal dopaminergic deficit is a slowly but steadily increasing phenomenon in the early phase of the disease [13, 14]. In RBD subjects who remained parkinsonism free, 123I-Ioflupane uptake reduction was more pronounced in the putamen than it was in the caudate nucleus [13]. It can be assumed that even at an early, premotor stage of PD, when the individual SPECT-DaTSCAN result remains within the normal range, there may be a subtle asymmetry in the number of dopaminergic cells in the substantia nigra, and that this asymmetry is unmasked when the patient develops DIP. However, our results seem to exclude this possibility.

Conclusions

Our results have not confirmed the presence of a presynaptic nigrostriatal deficit which could be related to asymmetry of DIP.

Future directions

The factors responsible for the asymmetry of DIP symptoms should be sought in the postsynaptic part of the nigrostriatal dopaminergic system.

Conflict of interest: *None declared.*
Funding: *The study was sponsored by the Medical University of Lodz (grant 503/7-127-01/503-51-002)*
Ethics: *This study was a retrospective analysis of data, and ethical approval was not necessary for the preparation of this article.*

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