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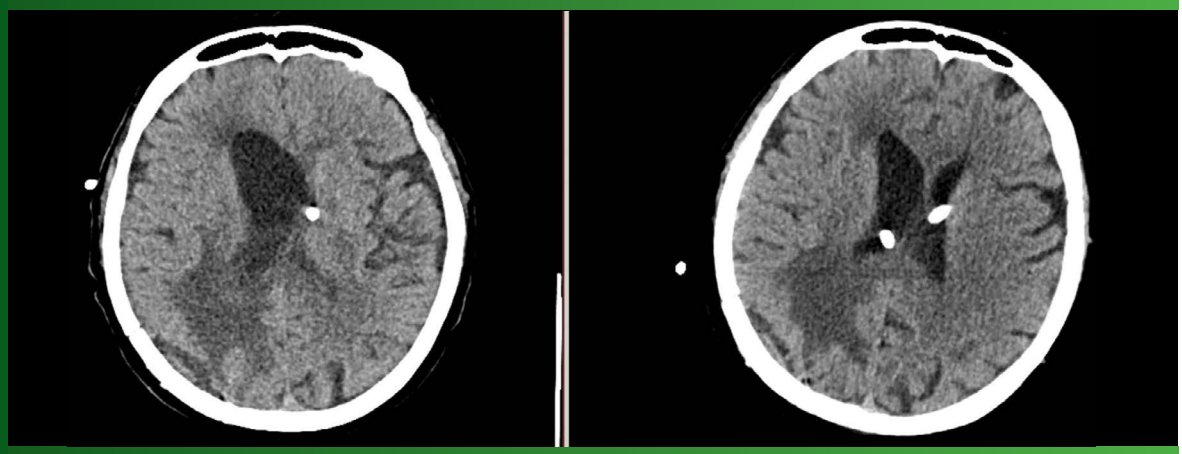

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EDITORIAL NOTE

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Message from the Editors to Our Reviewers – Thank you for Your Support

The Editors of the *Polish Journal of Neurology and Neurosurgery* (*Neurologia i Neurochirurgia Polska*) appreciate very much the assistance of our reviewers in making the Journal better forum for the neurological and neurosurgical research and education in Poland and beyond. The constructive reviews provided to our authors are extremely valuable. We understand the burden this work places on our reviewers. We are working hard to make the review process technically as easy as possible.

The Journal's national and international reviewers' panel has been substantially increased over the last two years. We are working to expand the pool of national and international reviewers both in the field of neurology and in the field of neurosurgery. If interested, please send us an e-mail or regular mail with your areas of expertise and interest, and a short bio. We have received positive comments from authors and reviewers in regards to handing the process of manuscript submissions and reviews through our new publisher, Via Medica.

We are grateful to all reviewers for their contribution to the works of the Journal. Those reviewers who have provided three or more reviews are indicated by an asterisk.

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Positron emission tomography neuroimaging in neurodegenerative diseases: Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis

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ABSTRACT

Neurodegenerative diseases are a growing problem of ageing societies. Their insidious onset, and the lack of reliable biomarkers, result in significant diagnosis delays. This article summarises the results of studies on the use of positron emission tomography (PET) in the diagnosis of Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. It focuses on clinical-pathogenetic aspects of individual diseases, as well as disease-specific patterns relevant in differential diagnosis and in assessing the risk of disease development and prognosis.

Key words: Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, positron emission tomography

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Introduction

Positron emission tomography (PET) is a nuclear functional imaging technique that enables an assessment of physiological parameters, such as metabolic rate, receptor density or protein deposition. The images are obtained with scanners detecting radioactive ligands usually administered intravenously (Tab. 1). Radiotracers used in PET imaging are mainly labelled with carbon-11 or fluorine-18. Carbon-11 labelled radiotracers have a short half-life time of 20 minutes, which requires a cyclotron on-site and restricts their use only to highly specialised hospitals. With a half-life time of 110 minutes, fluorine-18 labelled radiotracers can be manufactured off-site and transferred to the place of administration [1]. Although considerable information can be acquired from the PET functional image (especially if the functional signal is preserved), a detailed anatomical analysis may require normalisation by image fusion of PET and computed tomography (CT) or magnetic resonance imaging (MRI) [2].

Alzheimer's disease

Alzheimer's disease (AD) is a chronic neurodegenerative disease with an accumulation of amyloid-β (Aβ) and hyperphosphorylated tau proteins resulting in the formation of amyloid plaques (AP) and neurofibrillary tangles (NFTs). It is characterised by a progressive decline in memory functions, deterioration of other cognitive abilities (language functions, visuospatial abilities, complex tasks involving planning/handling), as well as changes in behaviour and personality. In 2015 dementia was estimated to affect 46.8 million people worldwide, with AD being its most common cause. This number is expected to double every 20 years [3].

PET in diagnosis of AD

The majority of PET studies in AD are performed with two groups of radioligands: biomarkers of neuronal dysfunction, and biomarkers of Aβ and tau protein depositions.

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Table 1. PET radioligands used in diagnostics of neurodegenerative diseases

PET radioligand (short names)	Target	Clinical utility
^{18}F-FDDNP	amyloid-β (Aβ) and tau-protein *assessing* Aβ and tau-protein depositions	diagnosis and evaluation of AD (*^{18}F-FDDNP*); differentiating between PSP and PD (*^{18}F-FDDNP*)
^{18}F-AV-1451 (T807), ^{18}F-T808, ^{18}F-THK-5105, ^{18}F-THK-5117, ^{18}F-THK-5351, ^{11}C-PBB3	tau-protein *assessing tau-protein depositions*	diagnosis of AD (*^{18}F-THK-5351*, *^{11}C-PBB3*); evaluation of AD (*^{18}F-AV-1451*, *^{11}C-PBB3*); differentiating between AD and CN/MCI (*^{18}F-THK-5351*, *^{11}C-PBB3*)
^{11}C-PiB, florbetapir, florbetaben, flutemetamol, ^{3}H-BF-227, ^{18}F-AZD4694 (^{18}F-NAV4694)	amyloid-β (Aβ) *assessing* Aβ depositions	diagnosis of AD (*^{11}C-PiB, florbetapir, florbetaben, flutemetamol*); differentiating between AD and CN/MCI or FTD (*^{11}C-PiB, florbetapir*); predicting the MCI-AD conversion (*^{11}C-PiB*)
^{11}C-MP4A	acetylcholinesterase enzyme *assessing the brain acetylcholinesterase activity*	diagnosis of AD (*^{11}C-MP4A*); differentiating between AD and DLB (*^{11}C-MP4A*)
^{18}F-DOPA, ^{18}F-FMT	amino acid decarboxylase *assessing striatal dopaminergic presynaptic function*	diagnosis and evaluation of PD (*^{18}F-DOPA, ^{18}F-FMT*); differentiating between PD and APS (*^{18}F-DOPA*)
^{11}C-CFT, ^{18}F-beta-CFT, ^{11}C-MP, ^{11}C-FE-CIT, ^{11}C-PE2I, ^{18}F-FP-CIT	dopamine transporter (DAT) *assessing DAT distribution*	diagnosis of PD (*^{11}C-CFT, ^{18}F-beta-CFT, ^{11}C-MP, ^{11}C-FE-CIT, ^{11}C-PE2I, ^{18}F-FP-CIT);* evaluation and prognosis of PD (*^{18}F-beta-CFT, ^{18}F-FP-CIT*); differentiating between PD and APS (*^{11}C-PE2I, ^{18}F-FP-CIT*); differentiating between PD and ET (*^{11}C-FE-CIT*); differentiating between MSA-P and MSA-C (*^{11}C-CFT*)
^{11}C-DTBZ, ^{18}F-AV-133 (florbenazine)	vesicular monoamine transporter 2 (VMAT2) *assessing VMAT2 distribution*	diagnosis of PD (*^{11}C-DTBZ, ^{18}F-AV-133*); differentiating between DLB and AD (*^{18}F-AV-133*); evaluation of cognitive performance in DLB (*^{18}F-AV-133*); evaluation of motor performance in PD (*^{11}C-DTBZ*)
^{11}C-raclopride, ^{11}C-n-methylspiperone, ^{11}C-FLB 457, ^{18}F-fallypride, ^{18}F-desmethoxyfallypride	D2 receptor *assessing postsynaptic dopaminergic function*	diagnosis of PD (*^{11}C-raclopride, ^{18}F-fallypride*); differentiating between PD and APS (*^{18}F-desmethoxyfallypride*); assessing the risk of developing "wearing-off" fluctuations (*^{11}C-raclopride*)
^{11}C-(R)-PK11195, ^{11}C-PBR28	translocator protein-18 kDa (TSPO) *assessing microglia activation*	differentiating between PDD and non-demented PD (*^{11}C-(R)-PK11195);* diagnosis of ALS (*^{11}C-(R)-PK11195*)
^{11}C-flumazenil	GABA-A *assessing GABA-ergic function*	diagnosis, evaluation and prognosis of ALS (*^{11}C-flumazenil*); differentiating between ALS and PLS (*^{11}C-flumazenil*)
^{11}C-deprenyl-D2	MAO-B *assessing astrocytosis activation*	diagnosis of ALS (*^{11}C-deprenyl-D2*)

PET — positron emission tomography; AD — Alzheimer's disease; PSP — progressive supranuclear palsy; PD — Parkinson's disease; CN — cognitively normal; MCI — mild cognitive impairment; FTD — frontotemporal dementia; DLB — dementia with Lewy bodies; ET —essential tremor; MSA-P — multiple systemic atrophy-parkinsonian; MSA-C — multiple systemic atrophy-cerebellar; PDD — Parkinson's disease dementia; APS — atypical parkinsonian syndromes; ALS — amyotrophic lateral sclerosis; PLS — primary lateral sclerosis

^{18}F-FDG

Neuronal dysfunction is mainly evaluated with ^{18}F-fluorodeoxy-glucose (^{18}F-FDG), a well-established biomarker of cerebral glucose metabolism. Glucose uptake in AD patients is characterised by hypometabolism in posterior cingulate-precuneas, posterior lateral and medial temporal-parietal association cortex and lateral frontal cortex [4–7] (Tab. 2). A more pronounced and extensive hypometabolism is present in early-onset compared to late-onset AD [8]. Interestingly, reaching the same severity of clinical dementia requires a greater hypometabolism in early- as compared to late-onset disease [8]. Both the aphasic (aphasic AD) and the posterior cortical atrophy (PCA) variant of AD (visuospatial AD), present different glucose uptake patterns when compared to typical AD (memory AD). A marked lateralisation of the hypometabolism to the left hemisphere has been found in the aphasic form of AD, while predominant posterior temporoparietal and occipital hypometabolism has been found in the visuospatial

Table 2. Glucose uptake patterns in neurodegenerative disorders

Disorder	Prevalent pattern		Anatomical distribution of glucose uptake patterns										
	Hypermetabolism	Hypometabolism	Cerebrum cortex				Basal Ganglia	Thalamus	Cerebellum	Brainstem	Anterior cingulate	Posterior cingulate	References
			Frontal	Parietal	Temporal	Occipital							
Alzheimer's Disease	-	predominantly in posterior regions: posterior temporoparietal association cortex and posterior cingulate cortex	↓	↓ (spared SMC)	↓ (posterior part)	Normal/↓	N	N	N	N	N	↓	68–73
Frontotemporal Dementia	-	predominantly in anterior regions: frontal lobes, anterior temporal cortex and anterior cingulate cortex	↓	N	↓ (TP)	N	N/↓[a]	N/↓[a]	N	N	↓	N	6, 53, 54
Dementia with Lewy bodies	-	occipitoparietal area with the preservation of the posterior cingulate region (cingulate island sign)	↓	↓	↓	↓ (PVC)	N/↓	↓	N	N	N	↓	9, 59, 60
Idiopathic Parkinson's Disease	dorsolateral putamen, globus pallidus, thalami, pontine, cerebellar, cortical motor area	dorsolateral prefrontal cortices and parietooccipital cortices	↓	↓	↓	↓	↑	↑	↑	↑	↓	N	88–91
Multiple System Atrophy	bilateral frontal and superior parietal cortices, bilateral thalamus	bilateral dorsolateral putamen, cerebellum and pons	↑	↑	↑/↓	↓	↓	↑	↓	↓	↓	N	60, 88, 89, 108, 109
Progressive Supranuclear Palsy	bilateral: cortical motor areas, parietal cortex, thalamus and caudate nuclei	brainstem (especially midbrain), midline frontals regions -	↑	↑	↓	N	↑	↑	N	↓	↓ (predominantly)	↓	60, 88, 89
Corticobasal Degeneration	-	asymmetrical, contralaterally to the most affected side: parietal cortices and basal ganglia	↓	↓	↓	N	↓	↓	N	↓	↓	N	88, 89, 104, 115, 116
Amyotrophic Lateral Sclerosis	midbrain, temporal pole, hippocampus and cerebellum	frontal, motor and occipital cortex	↓	↓	↑ (TP)	↓	↓ (↑ LGP)	N	↑	↑ (predominantly midbrain)	↓	N	136–138

LGP — Lateral Globus Pallidus; TP — temporal pole; SMC — sensory motor cortex; PVC — primary visual cortex; ↓ — decreased metabolism; ↑ — increased metabolism; N — normal; [a] in advanced stage

variant [9]. Additionally, the retention of a tau radioligand, ^{18}F-AV-1451, significantly differs between typical and atypical AD and also between visuospatial and aphasic (logopenic) AD [10, 11]. In a meta-analysis of ^{18}F-FDG PET studies with cognitively normal controls, the pooled sensitivity and specificity in distinguishing AD from healthy controls (HCs) were 86% and 86%, respectively [12]. ^{18}F-FDG PET imaging has a superior diagnostic accuracy in distinguishing AD from non-demented patients or individuals with mild cognitive impairment (MCI) compared to other diagnostic methods

such as clinical guideline, CSF biomarkers, MRI, CT and SPECT [13]. AD-related hypometabolism pattern correlates significantly with disease severity assessed with Mini-Mental State Examination (MMSE), Alzheimer's Disease Assessment Scale–Cognitive scales and Everyday Cognition scale [14, 15].

Aβ and tau tracers

Although Aβ and tau protein brain depositions are the neuropathological hallmarks of AD, neither of them is AD-specific. Positive Aβ scans are also present in dementia with Lewy bodies (DLB), cerebral amyloid angiopathy (CAA), and in up to 35% of cognitively unimpaired individuals > 60 years [16–18]. Positive tau protein scans are also seen in tau positive frontotemporal lobar degeneration (FTLD-tau), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and chronic traumatic encephalopathy. Interestingly, FTLD with TDP43 (FTLD-TDP), which is a non-tau pathology disorder, presents positive tau protein scans. This suggests an off-target binding of the radiotracers [19–24]. On the other hand, negative AP PET scans are obtained in rare forms of AD with unusual amyloid plaques that cannot be detected with commonly used Aβ tracers.

Developed in 1999, 2-(1-{6-[(2-[F-18]fluoroethyl)(methyl) amino]-2-naphthyl}ethylidene) malononitrile (^{18}F-FDDNP) was the first PET radiotracer to be used effectively in the visualisation of AD pathophysiology in living humans [25, 26]. It non-selectively binds to both AP and NFTs, but is less sensitive for tau deposits detection compared to further-mentioned radiotracers. Global brain ^{18}F-FDDNP uptake is significantly higher in AD patients compared to HCs. Its binding in the anterior cingulate and frontal region correlates inversely with MMSE score, while the neocortex uptake strongly correlates with cell losses in the hippocampus [27, 28]. A significantly lower global retention of ^{18}F-FDDNP has been shown in HCs compared to MCI and in MCI compared to AD [29].

Tau tracers

Post mortem histopathological studies have shown a stronger correlation of neuronal loss and MMSE score with NFTs compared to AP deposits [30, 31]. The group of tau protein radiotracers include ^{18}F-AV-1451 (T807), T808, ^{18}F-THK-5105, ^{18}F-THK-5117, ^{18}F-THK-5351 and ^{11}C-PBB3. High T807 binding is present in both MCI and AD patients, and is especially marked in the inferior temporal gyrus where its uptake correlates with MMSE and Clinical Dementia Rating scale sum of boxes (CDR-SOB) [32, 33]. Its use is however limited due to a significant off-target binding, including iron, neuromelanin, and MAO [34–36]. ^{18}F-THK-5351 retention differs significantly in AD compared to HCs or MCI and it correlates with neuropsychological tests in both MCI and AD patients. It also inversely correlates with the FDG uptake [37, 38]. ^{11}C-PBB3A neocortex retention is significantly higher in AD compared to HCs and its uptake in the frontal and temporo-parietal junctions correlates inversely with MMSE [39]. The short half-life time of this radiotracer restricts its clinical use, and a fluorine-18 labelled PBB3 is expected to be developed in the near future.

Aβ tracers

A retention of Aβ PET tracers highly correlates with brain biopsy findings [40, 41]. The first Aβ plaques PET radioligand was the Carbon-11-labelled Pittsburgh compound B (^{11}C-PiB) with a pilot human study performed in 2002 and the first peer-reviewed article published in 2004 [42, 43]. The ^{11}C-PiB retention in AD is most prominent in the frontal cortex, followed by the parietal, temporal and occipital cortex and the striatum, compared to HCs [43]. ^{11}C-PiB retention negatively correlates with glucose uptake but not with MMSE or CDR [43, 44]. Other Aβ amyloid tracers include fluorine-18-labelled radioligands such as florbetapir, florbetaben and flutemetamol, all approved for clinical use by the US Food and Drug Administration (FDA). An analysis of seven AD individuals showed a thorough agreement between visual reads of flutemetamol PET scans and histological brain biopsy findings [45]. In a meta-analysis of 19 studies, the pooled sensitivity and specificity rates in distinguishing AD from HCs for florbetapir were 89.6% and 87.2%, and for florbetaben 89.3% and 87.6%, respectively, while in a phase II trial with flutemetamol they were 93.1% and 93.3% [46, 47]. A prospective study of 211 patients suspected of early-onset dementia showed that the addition of flutemetamol PET imaging to clinical examination, medical history, laboratory tests, brain MRI and neuropsychological testing, increased the diagnostic confidence from 69% ± 12% to 88% ± 15%. The study resulted in a change of diagnosis in 19% and initiation of treatments in 37% of patients with AD [48]. In the early stage of the disease, amyloid PET imaging showed as high an accuracy in AD diagnosis as Aβ42/total tau or Aβ42/hyperphosphorylated tau CSF. A combination of CSF and PET biomarkers were not however able to increase the diagnostic accuracy [49]. In recent years both flutemetamol and florbetapir have become widely available in the US and Western Europe and have been used in a number of clinical trials. Other accessible Aβ selective biomarkers clearly differentiating AD from HCs are BF-227 and ^{18}F-AZD4694 (NAV4694) [50, 51].

PET in differential diagnosis of AD

Determining the cause of dementia is challenging, even for specialists. Accurate diagnosis is essential because each dementia subtype has a specific mechanism, treatment, family risk, and prognosis.

AD vs FTD

Frontotemporal dementia (FTD) is a neurodegenerative disease characterised by progressive deficits in behaviour, executive functions, or language. Its pathological hallmark is the degeneration of the prefrontal and anterior temporal cortices [52]. Cognitive impairment may be absent in the prodromal phase with only behavioural changes, which can lead to an

erroneous diagnosis of psychiatric disorder. The behavioural variant of FTD can also clinically overlap with the frontal variant of AD as both disorders develop behavioural changes. ^{18}F-FDG PET imaging in FTD patients shows hypometabolism predominantly in anterior regions: frontal lobes, anterior temporal cortex and anterior cingulate cortex, while in AD the hypometabolism is present in posterior regions including posterior temporoparietal association cortex and posterior cingulate cortex [6, 53, 54] (Tab. 2). The sensitivity and specificity rates for differentiating AD from FTD with ^{18}F-FDG PET imaging have been estimated at 99% and 65%, respectively [55]. Interestingly, ^{18}F-FDG PET imaging is superior to clinical assessment in differentiating AD and FTD by an experienced dementia specialist, reaching a diagnostic accuracy of 89.6% [56]. As Aβ protein depositions are not features of FTD, there is a significantly lower florbetapir uptake compared to AD [57]. A study performed in 62 AD and 45 FTLD patients showed a higher sensitivity rate for ^{11}C-PiB-PET visual read (89% *vs* 73%) and higher specificity for ^{18}FDG PET visual read (83% *vs* 98%) in differentiating AD from FTD [58].

AD vs DLB

DLB accounts for 20% of late-onset dementias. Its pathological hallmark is the presence of Lewy bodies within the neocortical and limbic regions and usually deposits of AP and NFTs. It is characterised by cognitive fluctuations, visual hallucinations and spontaneous features of parkinsonism. DLB may present a clinical overlap with AD in terms of cognitive impairment with executive and memory dysfunction and spontaneous parkinsonism. The glucose uptake pattern in DLB is characterised by a predominant occipito-parietal hypometabolism with the preservation of the posterior cingulate region presenting a 'cingulate island sign' on PET scans (Tab. 2) [9, 59, 60]. Revised criteria for the clinical diagnosis of probable and possible DLB have included ^{18}F-FDG PET imaging as a supportive biomarker. The sensitivity and specificity rates for differentiating DLB from FTD with ^{18}F-FDG imaging have been estimated to be 71% and 65%, respectively [55]. Since the deposition of Aβ is present in the majority of DLB patients, Aβ tracers are not useful in differentiating DLB from AD. However, high neocortical Aβ cortical deposits are associated with a shorter prodromal phase in DLB [16]. ^{18}F-AV-133, a biomarker of dopaminergic nigrostrial function, has a > 95% accuracy in differentiating DLB from AD and significantly correlates with cognitive performance in DLB patients [61, 62]. The combination of dopaminergic tracers and FDG has been shown to be useful in differentiating DLB from AD, Parkinson's disease (PD) and HCs [63]. Also, brain acetylcholinesterase (AChE) activity, measured with N-[11C]-methyl-4-piperidyl acetate (^{11}C-MP4A), reveals a significant difference between AD and DLB [64].

AD vs VD

Although vascular dementia (VD) is the biggest clinical challenge in differential diagnosis of AD, it is primarily evaluated by MRI [65]. ^{18}F-FDG PET scans reveal cortical and subcortical hypometabolism areas corresponding to signal changes in MRI.

In the most recent European Association of Nuclear Medicine (EANM) and European Academy of Neurology (EAN) recommendations for the use of brain FDG PET in neurodegenerative cognitive impairment and dementia, the panel agreed on recommending ^{18}F-FDG PET in diagnosing MCI due to AD, FTLD or DLB, in the diagnosis of atypical AD and pseudodementia, and in differentiating between AD and DLB, FTLD or VD, and between DLB and FTLD [66].

PET in prognosis of AD

Patients with MCI are at a higher risk for developing AD, with an estimated conversion rate of 10% to 15% per year [67]. In a one-year follow-up study performed in 37 MCI patients, all eight individuals who converted to AD showed reduced cerebral glucose metabolic rates in the inferior parietal cortex, in contrast to the non-converters [68]. Moreover, among APOE4 genotype positive groups, a prediction of conversion to AD reached the sensitivity of 100% and the specificity of 90%. Bilateral hypometabolism in the medial temporal cortex is also linked to a higher risk of conversion, while hypometabolism in the dorsolateral frontal cortex is present in stable MCI patients [69, 70]. The presence of the APOE4 gene in cognitively unimpaired individuals is linked with significant hypometabolism in posterior cingulate, parietal, temporal and prefrontal cortex as observed in the group with probable AD [71, 72]. A large meta-analysis that included six ^{18}F-FDG-PET studies with 280 patients showed a ^{18}F-FDG PET imaging sensitivity of 88.9% and specificity of 84.9% in the prediction of conversion to AD in patients with MCI. The results were more accurate than SPECT and structural MRI [73]. Positive ^{11}C-PiB scans in MCI patients at baseline strongly predicted conversion to AD, although negative ^{11}C-PiB scans did not exclude a further conversion [74–76]. ^{11}C-PiB PET imaging was able to clearly distinguish MCI from AD and MCI from HCs, and to differentiate those groups better than ^{18}F-FDG PET imaging [77–79].

A combination of markers including hippocampal volumetry (Hippo), ^{18}F-FDG PET, amyloid PET and CSF Aβ42 has a good predictive value in assessing the risk of conversion of MCI patients to AD. In a seven-year follow-up study, 73 patients were divided into four groups depending on biomarker positivity. The lowest conversion rate (5%) was reported for Aβ42(-),^{18}F-FDG-PET(-) Hippo(-), while the highest (100%) for concomitant Aβ42(+), ^{18}F-FDG-PET(+) and Hippo(+). The latter was also found to convert in the shortest time [80].

PET in progression and treatment of AD

^{18}F-FDG-PET has been established as a sensitive marker of disease progression of AD in a one-year follow-up study. On the other hand, ^{11}C-PiB-PET retention remained stable

in a two-year observation [4, 81]. A significant decline in AD-related glucose uptake pattern was observed in a one--year follow-up study in a non-treated group compared to a rivastigmine-treated group [82]. A similar outcome was obtained in a 24-week follow-up study with donepezil [83].

Parkinson's disease

PD is the second most common neurodegenerative disorder after AD. It is characterised by a dopaminergic neuronal loss in substantia nigra caused by intraneuronal proteinaceous inclusions, called Lewy bodies, mainly composed of α-synuclein. The diagnosis of PD is based on clinical criteria including bradykinesia, rigidity, resting tremor and postural instability. With disease progression, non-motor features such as cognitive decline, depression, psychosis, sleep dysfunction and dysautonomia may also be present [84, 85].

PET in diagnosis of PD

The most commonly used radioligands in PD PET studies are ^{18}F-FDG and dopamine-specific radiotracers that can be divided into three groups: biomarkers of dopamine (DA) synthesis (^{18}F-DOPA); biomarkers of synaptic dopamine transporters (DAT) (^{11}C-CFT, ^{11}C-MP, ^{11}C-FECIT, ^{11}C-PE2I, ^{18}F-FP-CIT) and vesicle monoamine transporters (VMAT2) (^{11}C-DTBZ, ^{18}F-AV-133); and biomarkers of postsynaptic dopaminergic function (D2/3 receptors, D2/3) (^{11}C-raclopride, ^{11}C-n-methylspiperone, ^{11}C-FLB 457, ^{18}F-fallypride, ^{18}F-desmethoxyfallypride) (Tab. 1). Other radioligands used in PD PET imaging include microglia activation biomarkers (^{11}C-(R)-PK11195) and AChE activation biomarkers (^{11}C--MP4P) [86, 87].

^{18}F-FDG

A PD-related pattern is characterised by hypermetabolism in the basal ganglia, ventral thalamus, pons and cerebellum with concurrent hypometabolism in the dorsolateral prefrontal, posterior parietal and occipital cortex [88-91] (Tab. 2). Its expression correlates positively with Hoehn and Yahr (H&Y) and Unified Parkinson's disease rating scale (UPDRS) motor scores [90].

Dopamine-specific tracers

Radiotracers assessing dopaminergic function are useful in PD diagnosis. There is a significant reduction of ^{18}F-DOPA uptake in the caudate nucleus and putamen and the ^{11}C-CFT uptake in the posterior putamen compared to HCs [92, 93]. Interestingly, a different ^{11}C-CFT distribution occurs in young-onset PD, where caudate nuclei are more spared compared to putamen. The late-onset subtype is characterised by a more uniform pattern [94]. As dopaminergic tracers' retention inversely correlates with motor disability (UPDRS motor scores in case of $_{18}$F-DOPA, $_{11}$C-CFT, $_{18}$F-FP-CIT and $_{18}$F-DTBZ), these may be useful in the evaluation of disease progression [94–96]. Furthermore, the retention of DAT (^{11}C-CFT) and VMAT2 (^{18}F-DTBZ) correlates with disease duration [94, 96].

Due to up-regulation of D2 receptors, D2/D3 tracer uptake is usually increased in PD [97]. A recent publication considering 18F-fallypride, one of the D2/D3 tracers, presented a significantly reduced retention in PD compared to HCs and a correlation between its uptake in the putamen and globus pallidus with UPDRS [98].

Non-motor dysfunctions in PD

PET has also been used in the assessment of psycho--behavioural and olfactory dysfunction. Limbic AChE activity correlates positively with cognitive and memory functions, but not with visuospatial functions [87]. While PD-dementia (PDD) is associated with a generalised cortical hypometabolism, PD-MCI patients develop hypometabolism in the temporoparietooccipital junction and the frontal cortex [99–101]. ^{11}C-(R)-PK11195-uptake, reflecting microglia activation, is significantly increased in cingulate, striatum and neocortex in PDD compared to HCs, and in the left parietal lobe in PDD compared to non-demented PD patients, and correlates inversely with MMSE score [86].

Hyposmic PD shows significantly reduced DAT (^{18}F-FP--CIT) binding in bilateral caudates and in left anterior and posterior putamen compared to normosmic PD patients [96]. Also the degree of DAT uptake (^{18}F-FP-CIT, ^{11}C-β-CFT) in the hippocampus, amygdala and striatum, VMAT2 (^{11}C-dihydrotetrabenazine) in the striatum and AChE activity tracer (^{11}C-MP4P) in the hippocampus, amygdala and neocortex correlates with the University of Pennsylvania Smell Identification Test (UPSIT) scores [87, 102, 103].

PET in differential diagnosis of PD

Due to its different prognosis and response to pharmacological and surgical treatment, it is especially important to differentiate PD from other diseases with parkinsonian features (known as atypical parkinsonian syndromes, APS), such as multiple system atrophy (MSA) and PSP, accounting together for 80% of misdiagnosed PD, as well as CBD and DLB [104].

Putamen hypermetabolism is one of the crucial elements of PDRP and the only feature distinguishing PD from APS [88, 89]. However, along with disease progression, the metabolism of the putamen normalises turning hypometabolic in the advanced stage, which may decrease its usefulness in differentiating a diagnosis [88, 89, 105]. An analysis of putamen-related parameters including posterior putamen binding, posterior-to-anterior putamen ratio, and posterior putamen-to-caudate with D2/3 receptor ligand (18F-DMFP) results in high sensitivity, specificity and accuracy (92%, 96% and 94%, respectively) in distinguishing PD from APS [106, 107].

PD vs MSA

MSA is characterised by a combination of parkinsonism, autonomic dysfunction, and cerebellar ataxia. Bilateral cerebellar and putaminal hypometabolism are distinguishing PET features of the disease [60, 88, 89]. Cerebellar hypometabolism is present in both patients with cerebellar dysfunction (MSA-C) and those without ataxia (MSA-P) [89]. Although not all MSA-P patients present cerebellar hypometabolism, it is rarely observed in other parkinsonian condition. Only a few MSA patients develop parietal hypometabolism, while it is a common finding in non-demented PD patients [108]. A significant correlation has been found between the degree of cerebellum and pons hypometabolism and cerebral ataxia and autonomic dysfunction. No such correlation has been observed between striatal hypometabolism and the severity of parkinsonism [109]. ^{18}F-FDG-PET sensitivity/specificity rates in the clinical diagnosis of MSA are 76%/98% with visual reading, and 96%/99% with statistical parametric mapping (SPM)-supported reading, respectively [89]. MSA-P patients present more pronounced DAT (^{11}C-CFT) reduction compared to MSA-C [110].

PD vs PSP

PSP is clinically characterised by a vertical gaze dysfunction, extrapyramidal features and cognitive decline. The specific glucose uptake pattern in PSP is characterised by bilateral reduction of metabolism in midline frontal regions and in the brainstem [60, 88, 89]. The evaluated sensitivity and specificity rates in the clinical diagnosis of PSP with the ^{18}F-FDG-PET visual reading are 60% and 96%, respectively, and with SPM-supported reading they account for 85% and 99% [89]. Caudate ^{18}F-dopa uptake is significantly lower in PSP compared to PD, and equally decreased in anterior and posterior putamen in PSP, in contrast to PD where the anterior putamen is relatively spared [92]. Since PSP is a tauopathy, tau radiotracers are useful in differentiating PSP from PD. ^{18}F-FDDNP shows a distinctive pattern at early disease stages and its binding in the frontal lobe correlates with the PSP rating scale (PSPRS) score [111]. High ^{18}F-AV-1451 uptake within the putamen, pallidum, thalamus, midbrain and dentate nucleus of the cerebellum is observed in PSP compared to HCs, and it also correlates with the PSP clinical severity score [112–114]. Compared to healthy individuals, PSP is also characterised by a higher ^{11}C-PBB uptake in globus pallidus, putamen, thalamus, subthalamus, midbrain, pons and peri-rolandic areas [23].

PD vs CBD

CBD is a neurodegenerative disease classified as a primary tauopathy characterised by progressive asymmetric rigidity and apraxia accompanied by other cortical and extrapyramidal dysfunction features [115]. The specific glucose uptake pattern in CBD is characterised by asymmetric basal ganglia and cerebral cortical hypometabolism, mainly expressed in frontoparietal area, contralateral to the clinically more affected side, and a bilateral occipital region hypermetabolism [88, 89, 116]. The sensitivity and specificity rates in the clinical diagnosis of CBD with ^{18}F-FDG-PET visual reading are 91% and 92%, respectively, and with SPM-supported reading they account for 91% and 99% [89]. The patterns of glucose and levodopa uptake differ in the early stages of CBD and PD [118]. Compared to HCs, CBD is characterised by a high retention of ^{11}C-PBB3 in the peri-rolandic areas, supplementary motor area, subthalamus and midbrain, with greater binding in basal ganglia contralaterally to the affected side [23]. Both ^{18}F-AV-1451 and ^{18}F-THK-5351 retention patterns are able to clearly differentiate CBD from HCs and AD, while ^{18}F-AV-1451 - from PSP [118, 119].

Interestingly, ^{18}F-FDG PET imaging has been found to be as predictive in risk stratification of APS as a one-year clinical follow-up. It was also superior to SPECT in differential diagnosis of APS [120, 121].

PET in assessment of treatment efficacy in PD

Long-term PD treatment results in late motor complications, such as fluctuations and dyskinesia. Patients who are at risk of developing 'wearing-off' fluctuations present significantly less expressed dopamine transporter activity in the putamen at baseline. Compared to individuals not experiencing 'wearing-off', they have been found to have a three times higher synaptic level of dopamine (measured with ^{11}C-raclopride) at one hour and no changes at four hours after oral administration of levodopa [122–124]. Marked DAT impairment in the posterior putamen at baseline is significantly associated with early appearance of levodopa-induced bradykinesia [125]. The long-time effect of PD pharmacological treatment assessed with PET studies showed a slower loss of striatal dopamine storage in patients treated with ropinirole compared to levodopa [126]. PD-related pattern (PDRP) decreases after subthalamotomy, deep brain stimulation (DBS) of the subthalamic nucleus (STN) and levodopa treatment, showing a correlation with clinical improvement after therapy [127, 128]. PET studies have been introduced into clinical trials including gene or cell therapy, but their outcomes do not always correlate with clinical improvement [129].

PET in prognosis of PD

Dysfunction of nucleus accumbens and orbitofrontal cortex on the clinically intact side, presented with reduced dopamine transporter radiotracer (^{11}C-CFT) uptake, positively correlates with the interval of developing bilateral parkinsonism [130]. Idiopathic rapid eye movement sleep behaviour disorder (iRBD) is considered to be one of the predictors of developing PD. In a clinical follow-up study of 10 iRBD patients and 10 HCs the phenoconversion to PD/DLB was more likely in individuals with high PDRP at baseline. In contrast, the iRBD patients who developed MSA 2–4 years later had

not expressed the PDRP at baseline [131, 132]. De novo PD patients with RBD present more pronounced hypometabolism in posterior cortical regions and anterior cortical regions of the more affected side, as well as a dopaminergic impairment of caudate nuclei and putamen measured with DAT uptake compared to non-RBD PD patients [133, 134]. Interestingly, iRPD patients present a significantly higher putamen/caudate ratio than both RBD-PD and non-RBD PD [134].

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease affecting the upper and lower motor neuron resulting in progressive neuromuscular weakness. The pathogenesis of the disease still remains unclear. Approximately 50% of patients develop language and executive dysfunction in the course of the disease, while 15% develop FTD (FTD-ALS) [135].

PET in diagnosis of ALS

^{18}F-FDG

The majority of ALS PET studies have been performed with ^{18}F-FDG. ALS glucose-uptake pattern is characterised by hypometabolism in frontal, motor, and occipital cortex and hypermetabolism in cerebellum, midbrain, temporal pole and hippocampus [136–138]. In a study with 195 ALS patients, significantly more expressed hypometabolism in left motor and premotor cortex was present in bulbar as compared to spinal onset patients [137]. In another study with 13 bulbar and 19 spinal onset patients, similar patterns were observed, but with no significant difference between the two groups. In ALS patients with spinal onset, there was a relative hypermetabolism in the right midbrain compared to HCs [136]. No meta-analysis of the sensitivity and specificity in discriminating ALS patients from controls has been performed to date. A one-year follow-up study performed in 195 ALS patients and 40 controls showed a sensitivity of 95.4% and specificity of 82.5% in discriminating both groups with ^{18}F-FDG imaging at baseline [137].

Other tracers

A significantly lower uptake of a GABA-A biomarker (^{11}C-flumazenil) has been found in the prefrontal, parietal, visual association and left motor and premotor cortex of ALS patients compared to HCs [139]. This may be due to the loss or dysfunction of inhibitory GABA-ergic neurons in ALS patients. Compared to HCs, sporadic ALS (sALS) show decreased cortical ^{11}C-flumazenil uptake predominantly in the premotor regions, motor cortex and posterior motor associated areas. Patients with ALS-linked D90A SOD1 mutation show a decreased radiotracer uptake in the left frontotemporal junction and anterior cingulate of the dominant hemisphere [140]. ^{11}C-flumazenil uptake in sALS correlates with upper motor neuron (UMN) damage, but not with revised ALS functional rating scale (ALSFRS-R), while in ALS SOD1 D90A homozygotes it correlates with ALSFRS-R and disease duration, but not with UMN damage. Patients harbouring a C9orf72 dynamic mutation, the most frequent genetic cause for ALS, present relatively more expressed hypometabolism in the thalamus and posterior cingulate compared to C9orf72-negative individuals [141]. In a study performed in 70 ALS patients (11 C9orf72-positive, 59 C9orf72-negative, 20 HCs), the sensitivity, specificity, and accuracy rates in distinguishing each patient group from HCs were 89.8%, 85.0%, and 88.6% in C9orf72-negative ALS, and 90.9%, 100%, and 96.8%, in C9orf72-positive cases, respectively [141]. Microglia activation, typically increased in ALS motor system, can be assessed with ^{11}C-(R)-PK11195 and ^{11}C-PBR28 radioligands. In a group of 10 ALS patients and 14 HCs, a significantly higher ^{11}C-(R)-PK11195 binding was found in motor cortex, pons, dorsolateral prefrontal cortex and thalamus in ALS patients compared to HCs. There was a correlation between radiotracer uptake in the motor cortex and UMN damage [142]. A significantly increased ^{11}C-PBR28 binding was also observed in the precentral gyrus of ALS patients compared to HCs [143]. ^{11}C-PBR negatively correlated with ALSFRS-R scale and positively with UMN damage, but there was no correlation with disease duration [143]. Bulbar onset patients showed increased ^{11}C-PBR uptake in the brainstem while limb onset in the precentral gyri [143]. Neuronal loss in the central nervous system in ALS patients is accompanied by actrocytosis. As MAO-B is primarily located in astrocytes, actrocytosis activation can be measured with MAO-B radiotracers such as ^{11}C-deprenyl-D2 (^{11}C-DED). A significantly increased binding of ^{11}C-DED has been observed in the pons and white matter of ALS patients compared to HCs [144].

PET in differential diagnosis of ALS

ALS vs FTD-ALS

FTD-ALS patients present more expressed hypometabolism including bilateral premotor, frontal, anterior prefrontal cortex with left predominance, lateral prefrontal and orbitofrontal cortex compared to ALS cognitively normal individuals. Significantly different patterns are also observed between cognitively normal and impaired ALS patients not fulfilling FTD criteria and cognitively impaired non-FTD ALS and ALS-FTD [145]. FTD-ALS patients present hypometabolism in the frontal area, while FTD alone have hypometabolism both in the frontal and temporal areas with a more symmetric pattern presented in FTD-ALS patients [146].

ALS vs PLS vs PMA

There is a significantly more expressed hypometabolism in the prefrontal cortex and posterior cingulate of ALS compared to primary lateral sclerosis (PLS) patients. It is also significantly less expressed in the primary sensorimotor cortex of PLS compared to ALS. The sensitivity and specificity rates allowing a distinction between PLS and HCs are 57.1% and 100%, respectively [141]. ^{11}C-flumazenil binding in anterior frontal and orbito-frontal regions was relative lower in both sALS

and D90A SOD1 ALS patients compared to PLS [147]. The glucose-uptake pattern in progressive muscular atrophy (PMA) did not differ from classic ALS, except for a less expressed hypometabolism in the motor cortex and the thalamus [141].

PET in prognosis of ALS

Extensive hypometabolism in the prefrontal or anterior temporal areas is associated with a significantly shorter survival in C9orf72-negative ALS patients [141]. As mentioned before, a reduced ^{11}C-flumazenil uptake in SOD1 D90A homozygotes has been shown to correlate with disease duration [140]. A significantly increased uptake of an oxidative stress biomarker, ^{62}Cu-ATSM, in the bilateral cortices around the central sulcus has been observed in ALS patients compared to HCs. It negatively correlated with ALSFRS-R [148].

Conclusion

PET imaging is a useful diagnostic tool in the assessment of various neurodegenerative diseases (Tab. 2). Specific glucose uptake patterns observed in AD and in other dementias enable physicians to diagnose and differentiate these disorders with high degrees of sensitivity and specificity. A group of accessible Aβ and NFTs radiotracers present high uptake in AD. ^{18}F-FDG-PET imaging can help predict MCI-AD conversion. The glucose uptake patterns characteristic for PD and APS permit the distinction of a number of disorders with parkinsonian features.

This is especially important in cases with different prognoses and responses to treatment. Dopamine radiotracers correlate well with disease severity and can predict further drug-induced motor implications. ^{18}F-FDG and ^{11}C-flumazenil imaging seems to be helpful in the diagnosis of ALS and in differentiating it from PLS as both diseases differ in prognosis.

In recent years, PET imaging has become widely accessible not only in scientific but also in clinical settings. The use of PET in the diagnostic process of neurodegenerative diseases provides the opportunity to decrease diagnosis delay, increase diagnostic confidence, and monitor treatment efficiency.

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Vitamin D as an immune modulator in multiple sclerosis

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Abstract

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disorder of the central nervous system. The disease is characterised by inflammation with extensive immune infiltration, demyelination, axonal loss and damage of oligodendrocytes, presumably auto-immune in nature. The influence of environmental factors on the development and activity of MS has been known for a long time. Vitamin D and sun exposure are among the most important ones. Both serum vitamin D level and sun exposure independent of vitamin D production are correlated with epidemiological and clinical parameters of MS, and the impact of vitamin D on immune parameters has been clearly confirmed in experimental studies. Nevertheless, the impact on clinical aspects is inconclusive, especially when the influence of supplementation is assessed. In this work we review the state of knowledge regarding the effect of vitamin D on immune cells subsets in relation to experimental and clinical studies.

Key words: multiple sclerosis, vitamin D, supplementation, T cells, B cells, dendritic cells, macrophages
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Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disorder of the central nervous system (CNS). The disease is characterised by inflammation with extensive immune infiltration, demyelination, axonal loss and damage of oligodendrocytes. The precise cause of MS remains unknown, but it is considered to be an autoimmune disease. A key role is played by T-lymphocytes, which after activation outside of the CNS pass through the blood-brain-barrier (BBB). T cells can contribute to CNS damage directly via cell-cell death or via soluble mediators including cytokines or proteases. Many studies suggest that B cells are equally important in MS pathogenesis. The presence of immunoglobulinG oligoclonal bands in the cerebrospinal fluid (CSF) of MS patients is a biomarker for disease and antibodies play a crucial role for demyelination in experimental autoimmune encephalomyelitis (EAE) [1]. The prevalence of MS is greater at higher latitudes, and tends to peak in areas with fewer sunny days. Traditionally, this prevalence was explained by a low exposure to ultraviolet light and/or diet, but several studies have shown that it is mainly the result of a lack or small amount of vitamin D [2, 3]. Vitamin D is an immunomodulator affecting both the innate and the adaptive immune system which is important in the development and activity of MS. The impact of vitamin D on immune parameters is evident *in vitro*, while the effects on the clinical aspects are inconclusive, especially when the effect of supplementation is assessed. In this work, we review current knowledge on the effect of vitamin D on immune cells subsets in relation to *in vitro* and *in vivo* studies. In this review, the term 'vitamin D' is used in relation to 25(OH)D or 1,25(OH)2D3, unless otherwise stated.

Vitamin D

Vitamin D is a pro-hormone belonging to the category of fat-soluble group of vitamins. It is primarily responsible for maintaining calcium homeostasis by facilitating absorption and utilisation of minerals and acts toward bone formation and homeostasis [4, 5]. This vitamin has also a much broader effect, as evidenced by the presence of its receptor in many organs and tissues [6]. The main sources of vitamin D are sunlight, diet, and supplementation. Vitamin D in the skin is present in the form of pro- vitamin D3 (7-dehydrocholesterol) and is converted to pre-vitamin D3 photochemically by ultraviolet B (UV-B) rays from the sun and subsequently converted to

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vitamin D3 by isomerisation. Foods rich in vitamin D include fatty fish (e.g. salmon, mackerel), cod liver oil, and, in small amounts, eggs. Relative to sun exposure, diet is a poor source of vitamin D. Vitamin D3 from the skin, food, or supplements is transported to the liver by vitamin D–binding proteins, where it is converted to 25(OH)D3 (calcidiol) through the process of hydroxylation. In the kidneys, 25(OH)D3 goes through a second hydroxylation to 1,25(OH)2D3 (calcitriol) which is the active metabolite. 1,25(OH)2D3 mediates its biological effects by binding to intracellular vitamin D receptor (VDR), which is a nuclear receptor that acts as a transcription factor. The binding 1,25(OH)2D3 with VDR leads to its heterodimerisation with the retinoid-X receptor (RXR), resulting in modulation of vitamin D responsive gene expression by translocation of heterodimer complex (1, 25 (OH)2D3-VDR/RXR) to nucleus, and its recruitment on vitamin D response elements (VDRE) of target genes. Depending on the site of recruitment of VDR, 1,25(OH)2D3 may regulate protein expression of target vitamin D-sensitive genes involved in diverse cellular processes. This includes cellular growth, proliferation, differentiation, apoptosis, oxidative stress and membrane transport [4, 6, 7]. A detailed review of the relationship between VDR and immune cells in multiple sclerosis was presented recently by Lu et al [8]. Thus, vitamin D affects the metabolism of various tissues and also has a significant influence both on innate and adaptive immunity. Because all immune cells express VDR, (e.g. macrophages, dendritic cells, T cells and B cells), vitamin D's effect on immunity via VDR leads to a shift in the immune response toward anti-inflammatory [7–9].

Impact of vitamin D on immunity cells

Dendritic cells (DCs) — Dendritic cells are the main antigen-presenting cells (APCs). Their function is to take up foreign antigens and present them as peptides to T cells on the human leukocyte antigen (HLA) molecules. DCs are predominantly found in an immature state in peripheral tissues. Upon encountering a foreign antigen, they mature and migrate to the lymphoid tissues to stimulate antigen-specific T cells. Depending on the cytokines secreted by the DC, the T cells will differentiate into effector cells with appropriate pro- or anti-inflammatory properties [10]. As 'professional' APCs, DCs play a key role in the pathogenesis of MS and EAE, in both mediating immune responses and inducing immune tolerance [11]. DCs constitutively express VDR and in the presence of 1,25(OH)2D3 remain in an immature-like tolerogenic state. This is characterised by inhibiting upregulation of the expression of MHC class II, CD40, CD80, and CD86 plus decreased production of pro-inflammatory IL-12 and TNFα and increased anti-inflammatory IL-10 production. 1,25(OH)2D3 can only induce this tolerogenic phenotype in DCs when it is added before their maturation [12, 13]. These tolerogenic DCs induce the differentiation of T regulatory (Treg) cells. Furthermore, they specifically induce apoptosis in autoreactive T cells, while not affecting the proliferation of other T cells [14, 15]. *In vitro* studies have confirmed that vitamin D inhibits DCs differentiation and maturation. However, the mechanism of Treg induction by DCs is not entirely clear. Recent studies have indicated that this depends on the type of DCs and there may be various mechanisms leading to the formation of Treg [16]. In EAE, both *in vivo* administration of vitamin D, and transfer of vitamin D-induced tolerogenic DCs, leads to a significant increase in the percentage of CD4(+) CD25(+) Foxp3(+) regulatory T cells and IL 10 production, as well as a decrease in the number of autoreactive T cells. Moreover, it significantly decreased the incidence of EAE and also reduced its severity [17–19]. Tolerogenic DCs are a very interesting direction of therapeutic research in MS, and currently the use of tolerogenic DCs generated with 1,25(OH)2D3 is being tested [20].

Macrophages — Macrophages are main phagocytic cells and they are also important APCs. In a normal immune response, they produce inflammatory mediators and recruit other immune cells to eradicate the pathogen. Macrophages can be divided into two categories: M1 and M2 macrophages. M1 macrophages produce pro-inflammatory mediators such as nitric oxide, TNFα, IL-23, IL-12, and IL-1β, whereby they kill pathogens and promote the polarisation of T helper (Th) cells to proinflammatory T helper 1 and 17 cells (Th1, Th17). On the other hand, M2 macrophages produce the anti-inflammatory cytokine IL-10 and are important in wound repair and restoring tissue homeostasis. In autoimmune diseases, macrophages are hyperactivated and produce more pro-inflammatory cytokines, suggesting a dysregulated balance between M1 and M2 cells [16, 21]. Vitamin D has dual roles in the differentiation and activation of macrophages. In the early stages of infection, 1,25(OH)2D3 stimulates differentiation of monocytes into macrophages and enhances the antimicrobial activity of human monocytes and macrophages. This pathway is vitamin D dependent and is not induced if the level of vitamin D is not sufficient [21–24]. Vitamin D also promotes the production of anti-inflammatory IL-10 and decreases the production of pro-inflammatory IL-1β, IL-6, TNFα, RANKL, COX-2, and nitric oxide. Finally, 1,25(OH)2D3-treated macrophages have been shown to reduce T cell stimulatory capacity [16, 22, 24]. In EAE, Nashold et al showed that vitamin D decreases macrophage accumulation in the CNS of mice, but flow cytometric analysis detected no significant differences between the groups with or without vitamin D suplementation, with respect to T cells or B cells or macrophages in draining lymph nodes or spinal cords [25].

T cells — T-cells consist of different subgroups such as CD4+ T-helper cells, cytotoxic CD8+ T-cells, regulatory T-cells, natural killer T cells (NKT) and gamma-delta T-cells. Currently, it is hypothesised that an imbalance between pro-inflammatory Th1/Th17 cells and Tregs is the crucial factor in the immunopathogenesis of MS. Vitamin D may act by restoring this balance, thereby restoring immune

homeostasis. This is related to the presence of VDR on Tcells [1, 26].

CD4+ T Cells

Th1 and Th2 - Classically, CD4+ T cells were subdivided into two classes: Th1 cells (with proinflamatory properties) and Th2 cells (with anti-inflammatory properties). 1,25(OH)2D3 inhibits the proliferation and differentiation of Th1 cells and enhances the expression of PD1, PD-L1 and CTLA4, inhibitory markers on $CD4^+$. In addition, it suppresses the production of proinflammatory cytokines mediated by Th1 cells and reduces IL-2, IL-6, IFN-γ, IL-17, and IL-22 secretion [24]. On the other hand, the activity of immune responses mediated by Th2 cells including the secretion of IL-3, IL-4, IL-5, IL-10, IL-13 has been enhanced by vitamin D.

It has been suggested that the impact of vitamin D on immune reactions is by promoting the Th2 cells response and suppressing the Th1 cells immune activity [26–28]. In EAE, vitamin D affects Th1 and Th2 cells and Th1/Th2 cytokine synthesis inhibiting EAE induction and significantly decreases its activity [17, 29–31]. Mayne et al showed that vitamin D acts directly on pathogenic CD4(+) T cells to inhibit EAE through the nuclear VDR. Vitamin D failed to inhibit EAE disease induction in chimeric mice lacking a functional VDR in haematopoietic cells and in T lymphocytes [30]. In another study, 1,25(OH)2D3 treatment significantly reduced the clinical severity of EAE within three days, decreasing chemokines levels and monocyte trafficking [31]. Studies carried out in MS patients have had ambiguous results. Mahon found that vitamin D supplementation significantly increased serum transforming growth factor-beta. Tumour necrosis factor (TNF)-alpha, interferon (IFN)-gamma, and interleukin (IL)-13 were not different following vitamin D supplementation [32]. However, an open-label randomised prospective controlled 52-week trial in patients with MS treated with escalating vitamin D doses up to 40,000 IU/day over 28 weeks showed that T-cell reactivity and proliferation dropped significantly in treated patients over the treatment period, while no change was seen in controls. However, cytokines profiles did not change significantly during the study [33]. A similar result was found in a study with a short term (24 weeks) supplementation of vitamin D in patients with clinically isolated syndrome (CIS) and controls. No significant differences were observed in the concentrations of IL-10, IL-17 and IFN-gamma produced followed stimulation of peripheral blood mononuclear cells (PBMCs) in any treatment arm. Moreover, no significant reduction in the frequency of proinflammatory CD4 T cells was seen [34]. Only Ashtari et al showed that in RRMS patients IL-10 serum level increased significantly after taking high-dose vitamin D3 for three months [35].

Th17 Cells - In most autoimmune diseases, Th17 cells are considered to be important drivers of disease pathogenesis. Th17 cells have proinflammatory properties and are characterised by the production of cytokines such as IL-17A, IL-17F, TNFα, proinflammatory cytokine granulocyte macrophage colony–stimulating factor (GM-CSF) and expression of the specific transcription factor, retinoid related orphan receptor (ROR). They can also be distinguished based on the expression of the chemokine receptor CCR6, which directs migration toward the chemokine CCL20. Their differentiation can be driven by TGFβ, IL-6, and IL-1β, but they require IL-23 to become pathogenic Th17 cells [36, 37].

Together, Th1 and Th17 effector cells are considered to be the major inflammatory mediators in MS. Notably, MS serum levels of IL-17 correlate with disease severity [38]. Vitamin D inhibits the differentiation and activity of Th17 cells. The presence of 1,25(OH)2D3 inhibits differentiation naïve CD4+ T cells toward the Th17 lineage *in vitro* and the formation of Th17-related cytokines and transcription factors such as IL-17A, IL-17F, RORC, and CCR6 [16, 39]. Similar results have been reported in the EAE model. Mice treated with vitamin D had fewer Th17cells and lower IL-17 production than placebo controls. This was related to a reduction of EAE induction and activity [40, 41]. Recently, vitamin D's impact on the expression of some Th17 cell- related cytokines, chemokines and chemokine receptors was investigated in EAE. In EAE mice, the expression of IL-17, IL-23 P19, IL-23 P40, CCL20, CCL22 and CCR4 in spinal cord and IL-17 and IL-23 serum levels were significantly higher than that in the control group [42]. The results are not conclusive in patients with MS. Da Costa et al evaluated *in vitro* the ability of 1,25(OH)2D in modulating different Th17 cell subsets in MS patients in the remission phase. The 1,25(OH)2D reduced Th17-related cytokines (IL-1β, IL-6, IL-17, IL-22), as well as GM-CSF. Additionally, the proportion of both IL17+/IFNγ+ (CD4+ and CD8+) T cells and IL17+/IFNγ- CD8+ T cells was positively related with neurological symptoms, determined by EDSS score [43]. Also Bhargava et al demonstrated that vitamin D supplementation decreased IL-17 producing CD4+ T cells and effector-memory CD4+ T-cells in MS patients [44]. However, Smolders et al found no correlation between Th17 cells and vitamin D serum level in MS patients [45]. Moreover, a high dose of oral vitamin D3 supplementation did not affect Th17 cells in MS patients [46]. Additionally, a randomised, double-blind, placebo-controlled clinical trial did not show a significant decrease of serum IL 17 level after 12 weeks of vitamin D supplementation. This was a small study (94 patients) and vitamin D was an added therapy to IFN-beta treatment [47].

Similarly, a sub-study of a larger clinical trial exploring high dose (up to 14,000 IU/day) vitamin D supplementation, as an add-on therapy to interferon beta 1a in patients with RRMS, showed no difference in either IL-17 CD4+ or IFN-gamma CD4+ T cells at 48 weeks of observation [48].

Regulatory T cells (Tregs) - suppress the immune response. Tregs express forkhead transcription factor FoxP3 which has been identified as essential in preventing autoimmunity in several animal models. Additionally, T regulatory cells secrete anti-inflammatory cytokines IL-10, IL-35, transforming

growth factor-b (TGF-b), the inhibitory co-receptor CTLA4, and a high level of CD25 [39, 49]. They exert immunomodulatory effects on other immune cells such as macrophages, DCs, CD8+ T cells, and also other CD4+ T cells, thereby maintaining immune homeostasis [49]. In patients with MS, functional defects in FoxP3+CD4+ Treg cells have been described in peripheral blood T cells with a reduction of T cell immune response and a decrease of IL-10 production compared to controls [50, 51]. The impairment correlated with reduced FoxP3 expression in MS patient T cells [52]. In EAE, vitamin D induced the differentiation of Treg cells, while inhibiting Th1 and Th17 cell proliferation. In addition, 1,25(OH)2D3 promoted secretion of the anti-inflammatory cytokine, transforming growth factor beta1 (TGF-β1) but suppressed pro-inflammatory cytokines such as IL-17 [43, 49, 53].

Spanier et al found, interestingly, that vitamin D acts synergistically with oestrogen, causing a decreased EAE risk in a female-biased manner. Moreover, a synergistic impact of vitamin D and oestrogen in VDR-expressing CD4(+) T is essential to induce Helios(+)FoxP3(+) T cells and prevent autoimmune demyelinating disease [54]. This clinical study only partially confirmed the impact of vitamin D on Treg in MS patients.

One study showed that the capacity of the CD25+CD4+ Treg cells was correlated with serum 25-OHD levels in MS patients [45], although this association could not be substantiated upon vitamin D3 supplementation [46].

CD8+ Cytotoxic T Cells

CD8+ T cells contribute to the immune response by inducing apoptosis in abnormal cells in cases of infection or cancer, and CD8+ T cells have a higher expression of VDR than CD4+ T cells [9, 51]. In MS, CD8 T cells are the most frequent T cell subset in acute and chronic plaques. Moreover, oligoclonal expansion of CD8 cells were observed in CSF, and the blood of MS patients [55, 56]. Nevertheless, in EAE, Nashold et al detected no significant differences between the groups with or without vitamin D suplementation, with respect to CD4+ or CD8+ cells in draining lymph nodes or spinal cord [25]. In MS patients, Lysandropulos found that vitamin D can act directly on CD8+ T cells [50], and with 1,25(OH)2D3, CD8+ cells secreted less IFN-gamma and TNF-alpha and more IL-5 and TGF-beta [57].

B Cells

B cells play a crucial role in the immune response by the production of autoreactive antibodies, modulating antigen presentation reaction and cytokine secretion. Human B cells are able to respond to vitamin D. They constitutively express low levels of the VDR, which is up-regulated upon B-cell stimulation [58].

In MS immunopathogenesis, B cells are important, something underlined by the presence of IgG oligoclonal bands in the CSF of patients with MS, complement deposition in type II lesions in CNS and B cell follicular structures in the meninges. Moreover, they can play several different roles: production of autoantibodies, formation of B-cell follicles with germinal centre activity, antigen presentation, production of pro-inflammatory cytokines, and anti-inflammatory immune regulation (Breg cells) [1, 58].

The effect of vitamin D on B cells is still not completely clear. Several studies have suggested that vitamin D reduces the proliferation of B cells, induces their apoptosis, and decreases antibody production. Moreover, it has been shown that vitamin D promotes IL-10 production in human B cells [59–61]. Currently, the effect of vitamin D on the proliferation and function of B cells in MS is being discussed. It has been shown that *in vitro* vitamin D has several effects on B cells, which may be beneficial in MS: the inhibition of plasma cell generation, the inhibition of T-cell co-stimulation, and the enhancement of Breg cell activity [62]. Unfortunately, the inhibitory effects of vitamin D have not been confirmed *in vivo*. Despite a 12-week high-dose vitamin D supplementation and a significant increase in serum vitamin D level, a shift in B cell differentiation was not found. IgG levels in serum and CSF of patients with MS did not correlate with 25(OH) D concentrations [63]. Also, after 12 weeks of high dose vitamin D supplementation, patients with RRMS did not show differences in total plasma IgG and IgM levels [64]. Likewise, in a cohort of healthy controls and RRMS patients, there was no correlation between IL-10 producing B cells and serum vitamin D level [65].

Impact of vitamin D on clinical activity of MS

Vitamin D's impact on immunity in MS patients has been confirmed in many *in vitro* studies.

Also studies in EAE strongly suggest the protective role of vitamin D [16]. However, the results of a small number of clinical trials exploring various immunological outcomes in response to vitamin D supplementation in MS have been contradictory. On the basis of current data, it is difficult to determine the molecular immunological mechanism of vitamin D supplementation. It is not clear why human data are conflicting, but vitamin D3 status at enrollment, vitamin D3 dose, dose frequency, use of disease-modifying drugs, and the timing of sampling (season, oestrogen cycling in women) are all potential confounding factors. This is an interesting problem, because a similar situation was encountered when the assessment of MS clinical activity after vitamin D supplementation was evaluated. Several studies have consistently shown an inverse relationship between vitamin D levels and the frequency of relapses, disability progression, and occurrence of new brain MRI lesions [39].

However, the evaluation of these parameters after vitamin D supplementation has yielded conflicting results. These

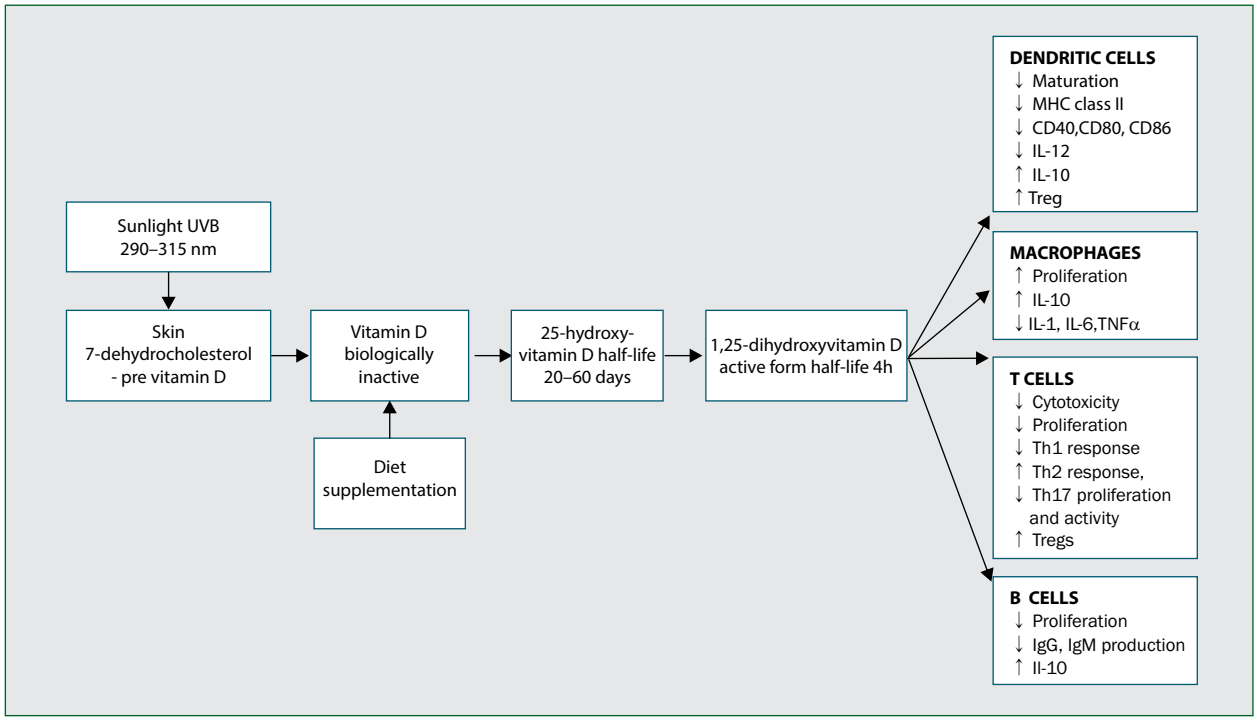

Figure 1. Sources, metabolism and potential immunomodulatory impact of vitamin D

results are difficult to compare because studies evaluating the effect of vitamin D supplementation on clinical parameters of MS have been generally small and with differing patterns. There have been studies with vitamin D alone, or with vitamin D as an add-on to a disease-modifying therapy, and highly varying doses of vitamin D have been used.

Because of that, in this review we arediscussing only double blind, placebo-controlled, randomised trials.

Stein et al investigated vitamin D's effect in RRMS patients. In this six-month, double blind, placebo-controlled, randomised trial, participants received either 1,000 IU vitamin D daily (low-dose) or 6,000IU (high dose). The results from this study did not show any effect of vitamin D in terms of clinical and MRI parameters [66]. Also Kampman et al found that suplementation of vitamin D did not result in beneficial effects on annualised relapse rates in a similar one-year, double-blind, placebo-controlled, randomised study in 66 MS patients [67].

Soilu-Hänninen et al did not find a reduction in the annual relapse rate although there was a tendency toward reduced disability accumulation as measured by EDSS and toward improved timed tandem walk. The authors stated that vitamin D add-on treatment to IFNbeta reduces MRI disease activity because patients in the vitamin D group showed fewer new T2 lesions and a significantly lower number of T1 enhancing lesions [68]. SOLAR was a randomised, double-blind, placebo-controlled, multicentre, phase 2 study. In this study, 229 patients were randomly assigned to vitamin D at a dose of 14,000 IU per day or a placebo as an add-on therapy to subcutaneous IFNbeta-1a. The percentage of patients with 'disease activity free' status (defined as no relapses, no EDSS progression, and no new Gd+ or T2 MRI lesions) was introduced as the primary endpoint. After 48 weeks of the study, no differences were found between the groups according to 'disease activity free' status, annual relapse rate, or EDSS score. Only the MRI parameters showed a significant reduction of the number of new, combined, unique active lesions in the vitamin D group [69]. Likewise, only the MRI parameters showed a significant reduction of the new or enlarged T1 and T2 lesions after vitamin D supplementation in another placebo-controlled study. In this study, 129 patients received 100,000 IU of vitamin D twice a month in addition to IFNbeta-1a over a 24-month period and no effect was found for clinical parameters [70]. Shaygannejad et al studied 50 patients in a 12-month, randomised, double-blind, placebo-controlled study and the patients received either vitamin D 8,000IU/day or a placebo with a disease-modifying agent. Mosayebi et al evaluated the effects of vitamin D3 supplementation at a dose of 300,000 IU/month *vs* placebo in 62 patients over a six-month period [71, 72]. The authors did not find any beneficial effect of vitamin D supplementation either on the clinical or the MRI outcome in patients with RRMS [73].

Because the evidence for vitamin D as a treatment for MS is inconclusive, it is not surprising that a meta-analysis did not find a significant association between vitamin D supplementation and the clinical outcome [74, 75]. However, it is worth noting that the tendency towards a favourable clinical response

Table 1. Overview of randomised controlled trials with vitamin D supplementation and clinical outcome in multiple sclerosis

Study	Study design	Supplementation dosage	Other medication	25(OH)D3 in treated group (nmol/L)	Clinical effect
Burton et al. (2010) [33]	Open, 52 weeks, Randomised 49 MS pts (*N* = 25 cholecalciferol, *N* = 24 placebo)	Escalating vitamin D3; 4,000–40,000 IU/day (p.o) Control 4,000 IU vitamin D3/day	calcium 1,200 mg/day, continuation of DMT	Mean 413	No effect on EDSS Trend toward reduced relapse rate
Stein M et al. (2011) [66]	RCT, 6 months 23 RRMS	High dose (initial 6,000 + 1,000 IU/day) vs low dose (1,000 IU/day) vitamin D2.	INF beta, GA	Median High dose 120 Low dose 69	↑EDSS and relapses in high dose group. No effect on T1Gd+ or T2 lesions
Mosayebi G et al. (2011) [72]	RCT, 6 months 62 MS pts, *N* = 28 cholecalciferol, *N* = 34 placebo	Vitamin D3 300,000 IU/month (i.m)	INF beta 1a	Mean ≈ 150	No effect on EDSS or Gd+ lesions
Soilu-Hänninen M et al. (2012) [68]	RCT, 12 months 66 RRMS pts, (*N* = 34 cholecalciferol, *N* = 32 placebo)	Vitamin D3 20,000 IU/week (p.o)	INF beta 1b	Mean 110 range (67–163)	↑T1Gd+ lesions No effect on T2 lesions, EDSS or relapse
Kampman M et al. (2012) [67]	RCT, 96 weeks 68 RRMS pts, (*N* = 35 cholecalciferol, *N* = 33 placebo)	Vitamin D3 20,000 IU/week (p.o)	Calcium 500 mg/day IFNbeta — 46% pts, GA 3% pts, natalizumab — 3% pts.	Mean 123 (113–133)	No effect on relapse rate, EDSS, MSFC and fatigue
Shaygannejad V et al. (2012) [71]	RCT, 12 months 50 RRMS pts, (N-25 calcitriol, 25 — placebo)	Escalating calcitriol: 0.25–0.5 µg/day (p.o)	Continuation of DMT: IFN beta 86.0% pts, statins 10.0% pts, immunosuppressive drugs 4.0% pts.		No effect on EDSS or relapses
Golan et al. (2013) [73]	RCT, 12 months 45 RRMS pts, ((*N* = 24 cholecalciferol, *N* = 21 placebo)	Vitamin D3 4,370 IU/day, controls 800 IU/day	INF beta	Mean High dose ≈ 120 Low dose ≈ 50	No effect on EDSS or relapses

DMT — disease-modifying therapy; EDSS — Expanded Disability Status Scale; GA — glatiramer acetate; Gd+ — gadolinium contrast enhancing lesions; IFNbeta — interferon beta; IU — International Units; MSCFC — Multiple Sclerosis Functional Composite; RCT — randomised controlled trial; RRMS — relapsing-remitting multiple sclerosis

was associated with a higher level of vitamin D. This indicates the need to determine the level of vitamin D during treatment. This is especially important because Bhargava et al found that MS patients have a diminished serologic response to vitamin D supplementation compared to healthy controls and have a lower increase in vitamin D levels with supplementation [76].

The status of vitamin D as the main factor affecting the development and activity of MS is unproven. It is one of the multi-factorial impacts of the environment, which has recently been emphasised. A high importance has been attributed to UV radiation.

It has been confirmed by epidemiological study that vitamin D and sun exposure are additive independent risk factors for MS development.

Further, the direct effects of sun exposure on MRI measures of neurodegeneration in MS, independently of vitamin D, have been reported [77, 78]. Studies in humans and mice suggest that UV radiation has an immunoregulatory property and this pathway is both vitamin D-dependent and vitamin D-independent [39, 79, 80]. The vitamin D-dependent pathway is considered the more important because humans obtain up to 80% of their vitamin D through sun exposure. UVB photons initiate a pathway of vitamin D production, from 7-dehydrocholesterol to the active form of vitamin D, as described previously. Several reviews have covered the immunomodulatory properties of vitamin D, particularly with reference to the regulation of cells proposed as being important to the development of MS [1, 2, 16]. However, additional factors should be taken into account. Firstly, the immunomodulatory properties of 1,25(OH)2D are dependent on genetic variation of the vitamin D regulating genes, CYP27B1 and CYP24A1 [81]. Moreover, immune cells have the enzymes to directly convert provitamin D or 25(OH)D to 1,25(OH)2D, and local concentrations, at the level of the cells, may be much higher than systemic levels [2]. Also vitamin D may regulate VDR-expressing nonimmune cells in the CNS. In one study of CIS patients, each 25 nmol/L increase in vitamin level was significantly associated with 7.8 mL higher grey matter volume, and there was a trend for an inverse relationship over 12 months between 25(OH)D levels and new brain lesions

and clinical relapses [82]. Vitamin D-independent pathways can be modulated by several molecules: *trans*-urocanic acid in the stratum corneum, DNA, RNA, lipids and tryptophan of keratinocytes, and antigen-presenting cells. All may initiate pathways involved in signalling from skin to immune cells in draining lymph nodes and tissues beyond. It has been shown that sub-erythemal amounts of UVR, as in narrowband UV phototherapy, can suppress both local and systemic immunity, measured functionally by reduced cell-mediated immune responses [79, 80].

In sub-erythemal UV-irradiated skin there are produced cathelicidin LL-37 and the α- and β-defensins in the absence of any inflammation. These peptides have modest anti-microbial activity but rather pleiotropic immunoregulatory properties and β-defensins via induction of T-regulatory cells can prevent and mitigate EAE [83–85]. Other studies have also demonstrated the effect of UV irradiation on an increase of Tregs and tolerogenic DCs both in EAE and in MS patients and in the maintenance of a pool of B-regulatory cells in the periphery [86, 87]. Recently, Breuer et al published a comprehensive review summarising the current knowledge regarding vitamin D and UVB light and concerning the clinical aspects of MS in epidemiological studies and clinical trials. The authors stressed that low vitamin D levels are associated with MS susceptibility and progression, although UVB light is involved in MS aetiology and progression independent of vitamin D [88].

In conclusion, numerous studies have suggested that vitamin D supplementation, and sun exposure independent of vitamin D production, may be protective against MS.

However, none of these can be treated alone as an active and sufficient treatment in MS. Further research is needed to establish how and when individuals with CIS or MS should be supplemented and to elucidate the beneficial mechanism of actions of UV exposure. This could help us to identify new targets that could offer wholly new avenues of MS therapy.

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Health-related quality of life and medication adherence in elderly patients with epilepsy

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ABSTRACT

Objective. Considering the high prevalence of epilepsy in the elderly and the importance of maximising their quality of life (QoL), this study aimed to investigate the relationship between medication adherence and QoL, and the mediating effects of medication adherence on the association between serum antiepileptic drug (AED) level and seizure severity with QoL in elderly epileptics.

Methods. In a longitudinal study, 766 elderly patients with epilepsy who were prescribed a minimum of one antiepileptic drug were selected by convenience sampling method. A Medication Adherence Report Scale (MARS-5) questionnaire was completed at the baseline. Seizure severity and QoL were assessed after six months using the Liverpool Seizure Severity Scale (LSSS) and the QoL in Epilepsy (QOLIE-31) questionnaires respectively. Serum level of AED was also measured at six-month follow-up.

Results. Medication adherence was significantly correlated with both seizure severity ($\beta = -0.33$, $p < 0.0001$) and serum AED level ($\beta = 0.29$, $p < 0.0001$) after adjusting for demographic and clinical characteristics. Neither QoL nor its sub-classes were correlated with seizure severity. In addition, a significant correlation was not observed between serum AED level and QoL. However, medication adherence was significantly correlated with QoL ($\beta = 0.30$, $p < 0.0001$). The mediating effects of medication adherence on the association between serum AED level ($Z = 3.39$, $p < 0.001$) and seizure severity ($Z = -3.47$, $p < 0.001$) with QoL were supported by the Sobel test.

Conclusion. This study demonstrates that medication adherence has a beneficial impact on QoL in elderly epileptics. Therefore, adherence to treatment should be monitored to improve their QoL.

Key words: epilepsy, medication adherence, seizure, quality of life, elderly
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Introduction

Epilepsy, a neurological disorder characterised by recurrent unprovoked seizures, is one of the most common chronic brain disorders globally [1]. Despite advances in the understanding of the pathophysiological mechanisms of epilepsy and the development of medical treatments in recent decades, people of all ages with this neurological disorder continue to

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be stigmatised by it [2]. Epilepsy is one of the world's longest-recognised medical conditions; it affects approximately 50 million people worldwide with nearly 80% of them living in developing countries [3]. The prevalence of epilepsy in the Iranian population is between 7.8–18/1,000 persons or approximately 1.4% of the population [4, 5], which is slightly higher than the reported prevalence of 5.8–8.4/1,000 persons in developed countries [1, 6]. This disease affects all ages, ethnicities and socioeconomic groups; however, its prevalence and incidence increase markedly in individuals over the age of 65 years, even more than they do in infancy, another high prevalence age. In fact epilepsy is the third most common neurological disease in the elderly, after stroke and dementia [7, 8]. Taking into account the future growth of the world's population aged > 60 years [9] due to increasing life expectancy, the prevalence of epilepsy is predicted to dramatically rise over the next few decades.

Medication adherence is a fundamental determinant of effective treatment [10] that is defined by the World Health Organisation as "the degree to which the person's behaviour corresponds to the agreed recommendations from a health care provider" [11]. Epilepsy has been successfully controlled with medication adherence, and most people with epilepsy (almost 70% of patients) can become seizure-free by taking one anti-seizure medication daily, called an anti-epileptic drug (AED) [12, 13]. Nevertheless, non-adherence to medication is a very common phenomenon in patients with chronic diseases [14-18] including epilepsy [18–23], which not only affects the individual's health but also the healthcare system. This leads to uncontrolled symptoms and substantial deleterious effects on the quality of life (QoL) and those patients can become a heavy burden on society and healthcare systems [24–26].

Elderly people with epilepsy generally respond well to AED treatment. Up to 80% of patients with late-onset epilepsy can be expected to remain seizure-free with AED treatment [27]; however, only 38–57% (average < 45%) of elderly epileptic patients have good adherence to AEDs [28]. Explanations for poor adherence in this population of patients include patient-physician discordance, complex medication regimen, the frequency of administration of multiple medications, disturbances of memory, specific beliefs about drugs, being depressed or anxious, and unusual times during the day to take the medication [25]. Although patient understanding of the optimal care, and improving their QoL, are problematic in epileptic treatment, it remains questionable whether adherence to AED can actually improve QoL in this population. The impact of AED therapy on the QoL in younger groups of patients has been previously reported [10, 29, 30] and positive and negative effects of AED therapy on QoL have been demonstrated [31]. However, the impact of AED treatment in terms of QoL among the elderly has not been well investigated.

Therefore, the primary aim of this study was to assess the QoL and its correlation with AED adherence among elderly patients with epilepsy. In addition, we aimed to evaluate the mediating effects of medication adherence in the relationship between serum AED level and seizure severity with QoL. To obtain more accurate information on AED adherence, both a self-reporting method (Medication Adherence Report Scale, MARS-5) and serum AED level measurement were used. The correlation between MARS-5 score and serum AED level and whether MARS-5 score can be replaced with serum AED level to predict the QoL in the elderly with epilepsy was also examined.

Material and methods

Study design and participants

This longitudinal study was carried out on 766 elderly patients with epilepsy referred to six neurology clinics between March 2014 and December 2015. The patients were recruited through convenience sampling. The subjects included males and females aged 65 years or above with a confirmed diagnosis of epilepsy according to the International League Against Epilepsy Criteria [32]. The subjects had the ability to perform daily activities, had been prescribed at least two AEDs, and had no major cognitive impairment (defined as a score of 23 or below on the Mental State Examination, MSE) or an acute psychiatric disorder diagnosed by a psychiatrist. Exclusion criteria were a history of drug abuse, diabetes, cardiovascular diseases, rheumatoid arthritis, malignant tumours, kidney dysfunctions and liver diseases, being in receipt of medications other than AEDs at the time of recruitment or throughout the follow-up period, and being unwilling to participate in the study.

All applicants were screened by a trained physician for eligibility according to these inclusion and exclusion criteria. All eligible participants were given a full explanation of the objectives and protocol of the study, and written informed consent was signed prior to enrolment. Demographic characteristics, clinical features and medication adherence were then collected from the participants. Six months later, the subjects were invited to attend the clinic to complete the questionnaires evaluating seizure severity and QoL. Blood samples were taken on the same day for the measurement of AED level as an objective assessment of AED adherence.

Instruments

Background information sheet and medical records

Demographic characteristics including age, sex, marital status, educational years, employment and monthly income (*High > $1,000; Intermediate = $500–1,000; Low < $500*) were collected by face-to-face interviews and recorded in the Background Information Sheet. The clinical features of the participants, including the type of epilepsy and the duration of the disease, were also collected from their medical records.

Medication Adherence Report Scale (MARS-5)

MARS-5 is a self-reporting and widely applicable questionnaire for the subjective assessment of medication adherence [33]. It consists of five statements of non-adherent behaviours (*I forgot to take my antiepileptic medicine, I altered the dose of my antiepileptic medicine, I stopped taking my antiepileptic medicine for a while, I decided to miss a dose of my antiepileptic medicine, I took less antiepileptic medicines than prescribed*) answered on a five-point Likert scale (1 = always, 2 = often, 3 = sometimes, 4 = rarely, 5 = never), giving an overall score that ranges between 5 and 25. According to the threshold, a MARS-5 score of 20 or above is considered as high adherence [14]. The concurrent validity and internal consistency of the MARS-5 questionnaire has been supported by previous studies [34]. The participants completed the MARS-5 questionnaire at the baseline.

Liverpool Seizure Severity Scale (LSSS)

The participants were asked to complete the LSSS questionnaire if they reported more than one week had elapsed since their last seizure. The LSSS questionnaire consists of 20 items rated on a Likert scale. A four-point Likert scale was used to respond to each item, with higher points indicating greater seizure severity. It has been demonstrated that LSSS is a valid and reliable instrument quantifying seizure severity that may also be used to evaluate changes in seizure severity over time [35]. Furthermore, the known-group validity showed subjects with severe seizure symptoms could be distinguished from those with minor seizure symptoms by LSSS [35].

Serum AED level

In order to measure serum concentrations at the six-month follow-up of the three most commonly used AEDs i.e. phenytoin, lamotrigine and carbamazepine, whole blood samples were taken prior to the next daily routine dose of drug. The serum was then separated, and AED concentrations were measured using a microparticle enzyme immunostimulatory assay kit (Abbott Axsym®, Abbott Laboratories, Abbott Park, IL, USA). The therapeutic dose range of AED which can prevent seizures effectively without toxic effects has been reported in detail [36]. The serum concentrations of AEDs were categorised into three groups based on the reference as 'below the therapeutic range', 'within the therapeutic range', and 'above the therapeutic range'.

Quality of Life in Epilepsy (QOLIE-31)

QoL was evaluated using a QOLIE-31 questionnaire, which was designed exclusively to assess an epileptic patient's QoL at six-month follow-up. It consists of 31 items in seven subclasses: seizure concerns, cognitive function, energy/fatigue, emotional wellbeing, social function, medication efficacy, and overall QoL [37]. The subscale scores range from 0 to 100 points, and the higher the score, the better the QoL. The overall score of QOLIE-31 can be calculated by weighting and summarising seven-dimension scores. The Persian version of QOLIE-31 has been shown to be a reliable instrument for assessing QoL in patients with epilepsy [38].

Statistical analysis

The results were expressed as mean ± standard deviation (SD) for quantitative data with normal distribution, and frequency (percent) for qualitative data. The analyses were performed in several steps. Firstly, Pearson correlation analysis was used to investigate the relationships between serum AED level, MARS-5 score, LSSS score, and overall QOLIE-31score. The relationships between serum AED level and LSSS score with the MARS-5 score were then evaluated by linear regression after adjusting for potential confounders (i.e. age, sex, marital status, education years, employment status, monthly income, type of epilepsy and disease duration). The relationships between independent variables (serum AED level, LSSS and MARS-5 score) and dependent variable (each sub-class of QoL and the overall score of the QoL) were also evaluated using multiple linear regression analysis, after controlling for potential confounders. Based on the Bonferroni correction, $p < 0.00625$ (0.05/8) is considered as significant for multiple comparisons between the eight regression models.

Lastly, structural equation modelling (SEM) was used to test the model and investigate whether seizure severity and serum AED level directly correlated with the QoL, or whether it was being mediated through other factors. Several fit indices, including chi-square statistics, Comparative Fit Index (CFI), Goodness-of-Fit Index (GFI), Tucker–Lewis Index (TLI), Normed Fit Index (NFI) and Root Mean Square Error of Approximation (RMSEA), were evaluated to determine the model fit. To interpret these indices, the following criteria were used: χ^2/df ratio < 2 (excellent); χ^2/df < 3 (good); χ^2/df < 5 (acceptable); ≥ 0.90 as good fit for CFI, GFI, TLI, and NFI; ≤ 0.08 as good fit for RMSEA[39]. Sobel test was also used to examine the significance of mediation effects. The descriptive analyses and regression models were performed using IBM SPSS version 21.0 software; SEM was conducted using AMOS 21.

Results

The demographic and clinical characteristics of the participants are set out in Table 1. The average age of participants was 73.9 ± 5.7 years, and more than half were female (54.7%). Most participants were married and had low levels of education. All patients received polytherapy with a minimum of two AEDs. Therefore, it is not possible to assess the effect of each type of AED on adherence. As shown in Table 1, more than two-thirds of participants had focal epilepsy (70.2%). Of the patients with focal epilepsy, 97 (18%) reported focal seizures without impairment of consciousness, and 68 (13%) patients reported focal seizures with impairment of consciousness.

All patients with generalised epilepsy reported convulsive seizures.

The mean overall score of the QOLIE-31 among the participants was 67.8 ± 20.5, with energy/fatigue the worst domain (59.3 ± 18.6) and medication efficacy the best domain (78.7 ± 24.1) (Tab. 1). Furthermore, nearly half of the participants (48.7%) had serum AED levels below the therapeutic range (i.e. categorised as non-adherent).

In the first step, we investigated the relationship between the variables. All of the correlation coefficients were statistically significant. In particular, MARS-5 score was positively correlated with serum AED level (r = 0.36, $p < 0.001$), and inversely correlated with LSSS score (r = –0.39, $p < 0.001$). In addition, a positive correlation was observed between QOLIE-31 score and MARS-5 score (r = 0.33, $p < 0.001$).

The relationships between the variables were then evaluated by multiple linear regression after adjusting for potential confounders. Table 2 shows the results from the regression models that evaluated the association between MARS-5 score with LSSS score and serum AED level. As shown in Table 2, MARS-5 score was significantly correlated with both LSSS (β = –0.33, $p < 0.0001$) and serum AED level (β = 0.29, $p < 0.0001$) after adjusting for confounders. In other words, LSSS and serum AED level were significant predictors of MARS-5 score and accounted for almost a quarter of the variation in the MARS-5 score.

The relationships between LSSS score, MARS-5 score and serum AED level with overall QOLIE-31 score and its domains are set out in Table 3. Neither overall QOLIE-31 score nor its sub-classes were correlated with LSSS score. Similarly, no significant correlation was observed between serum AED level and overall QOLIE-31 score and the scores in QOLIE-31 domains after adjusting for demographic and clinical confounders. However, MARS-5 score was significantly correlated with the overall score of QOLIE-31 (β = 0.30, $p < 0.0001$) and its domains.

After confirming the correlation between MARS-5 score and QOLIE-31 score, we tried to examine the proxy effects of MARS-5 on QoL using the SEM. The SEM analysis is graphically described in Figure 1. This model showed an acceptable fit. According to SEM analysis, all the goodness-of-fit indices indicated an acceptable fit, except for the χ^2 which was statistically significant ($p < 0.001$). However, the value of the χ^2/df ratio was good (3.105 < 5). The rest of the fit indices showed an acceptable fit, with CFI, GFI, TLI and NFI above 0.9, and RMSEA less than 0.08 (CFI = 0.974, GFI = 0.978, TLI = 0.957, NFI = 0.963, RMSEA = 0.052). The standardised coefficients of LSSS score on QOLIE-31 score (-0.015) and serum AED level on QOLIE-31 (0.021) were not significant, while the standardised coefficients of LSSS score on MARS-5 score (–0.316) and serum AED level on MARS-5 score (0.268) were significant. Furthermore, the mediating effects of MARS-5 score was investigated using the Sobel test. According to the Sobel test, LSSS (Z = –3.47, $p < 0.001$) and the serum AED level (Z = 3.39,

Table 1. Demographic and clinical characteristics of the participants (n = 766)

Age (years)	73.94 ± 5.77
Male, n (%)	347 (45.3%)
Married, n (%)	582 (76.0%)
Education (years)	8.91 ± 5.10
Employed, n (%)	276 (36.0%)
Monthly income, n (%)	
High (> $1,000)	162 (21.2%)
Intermediate ($500–1,000)	461 (60.2%)
Low (< $500)	143 (18.7%)
Epilepsy type, n (%)	
Generalised	228 (29.8%)
Focal	538 (70.2%)
Aetiology, n (%)	
Vascular	214 (28.0%)
Trauma	122 (15.9%)
Idiopathic/cryptogenic	430 (56.1%)
Type of medication, n (%)	
Phenytoin	506 (66.0%)
Lamotrigine	333 (43.5%)
Carbamazepine	305 (39.8%)
Oxcarbazepine	204 (26.6%)
Phenobarbital	148 (19.3%)
Topiramate	73 (9.5%)
Primidone	42 (5.5%)
Zonisamide	33 (4.3%)
Gabapentin	28 (3.7%)
Seizure frequency	3.4 ± 3.2
Disease duration (years)	17.71 ± 4.56
QOLIE-31score	
Seizure concerns	77.16 ± 35.05
Cognitive function	66.45 ± 42.93
Energy/fatigue	59.33 ± 18.63
Emotional wellbeing	61.27 ± 18.92
Social function	78.00 ± 21.61
Medication efficacy	78.72 ± 24.12
Overall quality of life	61.77 ± 19.99
Overall score	67.81 ± 20.50
LSSS score	54.91 ± 23.46
MARS-5 score	13.32 ± 6.48
Serum AED level, n (%)	
Below therapeutic range	373 (48.7%)
Within therapeutic range	295 (38.5%)
Above therapeutic range	98 (12.8%)

QOLIE-31 — *Quality of Life in Epilepsy Inventory-31*; LSSS — *Liverpool Seizure Severity Scale*; MARS-5 — *Medication Adherence Report Scale*.
The data is expressed as mean ± SD unless specifically indicated.
Seizure frequency was defined as the mean frequency of complex partial seizures per month during six months of follow-up

Table 2. The association between MARS-5 score and LSSS score as well as serum AED level

	B	SE	β	p^*
LSSS score	-0.09	0.009	-0.33	< 0.0001
Serum AED level	2.68	0.302	0.29	< 0.0001

AED — *antiepileptic drug*; LSSS — *Liverpool Seizure Severity Scale*; MARS-5 — *Medication Adherence Report Scale*; SE — *standard error*. The results were analysed by the multiple linear regression method after adjusting for age, sex, marital status, educational years, employment, income, epilepsy type and disease duration; *$p < 0.05$ was considered as statistically significant

$p < 0.001$) showed indirect effects on QoL score. This means that the MARS-5 score can mediate the relationship between LSSS and QOLIE-31, as well as the relationship between AED level and QOLIE-31 (Fig. 1). However, LSSS score and serum AED level did not directly affect the QoL.

Discussion

This study examined the associations among several variables that influence QoL in the elderly with epilepsy. We suggested a model for the effect of MARS-5 not only on the relation between seizure severity and QoL, but also on the relation between AED level and QoL. Our findings revealed that serum AED level, medication adherence, and QoL positively correlate with each other in elderly patients with epilepsy. Furthermore, we also found that increased seizure severity, as determined by LSSS score, was associated with decreased medication adherence among elderly patients with epilepsy.

The positive correlation between medication adherence and AED level suggests that the self-reported MARS-5 score could be suitable to assess AED adherence in the elderly with epilepsy, which is consistent with previous studies on

Table 3. Results from multiple linear regression analysis that evaluated the association between dependent (QOLIE-31 score and its domains) and independent (LSSS score, MARS-5 score and serum AED level) variables

Variables	LSSS		serum AED level		MARS-5	
	B (SE)	β	B (SE)	β	B (SE)	β
Seizure concern	0.07 (0.06)	0.05	–1.33 (1.84)	–0.03	1.37 (0.21)	0.25*
Cognitive function	–0.05 (0.07)	–0.03	4.61 (2.29)	0.07	1.58 (0.26)	0.24*
Energy/fatigue	–0.07 (0.03)	–0.08	0.57 (0.98)	0.02	0.57 (0.11)	0.20*
Emotional wellbeing	–0.04 (0.03)	–0.06	–0.90 (1.01)	–0.03	0.57 (0.12)	0.20*
Social function	–0.05 (0.03)	–0.05	–0.06 (1.16)	–0.01	0.75 (0.13)	0.23*
Medication efficacy	–0.05 (0.04)	–0.05	0.91 (1.28)	0.03	0.64 (0.15)	0.17*
Overall QoL	–0.01 (0.03)	–0.02	0.70 (1.05)	0.02	0.46 (0.12)	0.15*
Overall score	–0.04 (0.03)	–0.04	1.19 (1.05)	0.04	0.93 (0.12)	0.30*

QOLIE-31 — *Quality of Life in Epilepsy Inventory-31*; LSSS — *Liverpool Seizure Severity Scale*; MARS-5 — *Medication Adherence Report Scale*; AED — *antiepileptic drug*; QoL — *quality of life*; SE — *standard error*. The results were analysed by the Multiple Linear Regression method adjusted for age, sex, marital status, educational years, employment, income, epilepsy type and disease duration. *$p < 0.00625$ (Bonferroni correction with eight comparisons; 0.05/8 = 0.00625) was considered as statistically significant

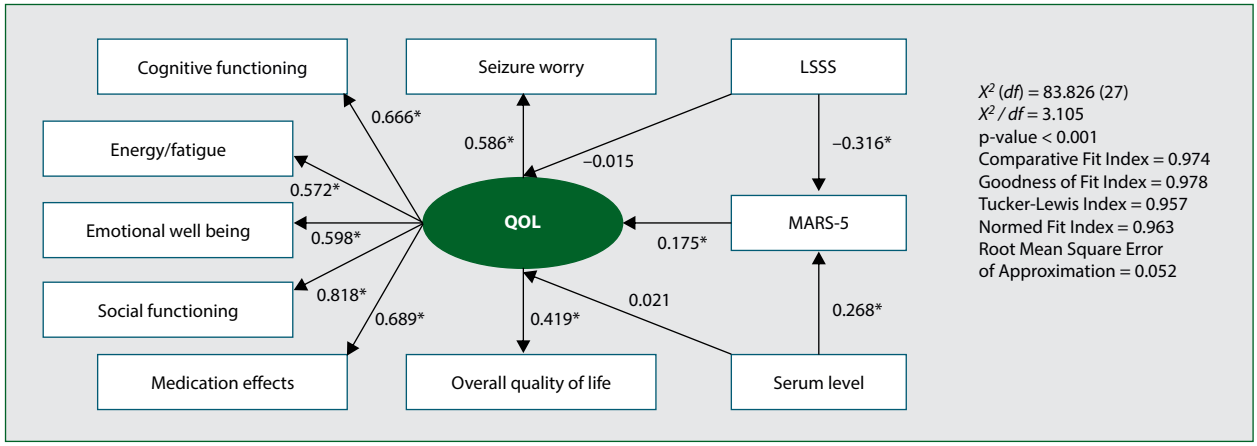

Figure 1. The proxy effects of MARS-5 score on the quality of life (QoL) in elderly patients with epilepsy. *$p < 0.001$; LSSS — *Liverpool Seizure Severity Scale*; MARS-5 — *Medication Adherence Report Scale*; QOL — *quality of life*

epilepsy treatment [25, 37]. Given that serum level measurement is invasive and costly, a MARS questionnaire could be used to evaluate patient adherence to treatment. However, in contrast to our findings, several studies on patients with chronic obstructive pulmonary disease (COPD) and children with asthma have suggested that the MARS-5 score is not an accurate self-reporting instrument to measure drug adherence in those patient cohorts [15, 16]. Furthermore, it has been reported that MARS-5 score is not an accurate instrument to measure drug adherence in hypertensive patients [14]. The contradictions observed between our results and those in the abovementioned studies might be due to the type of disease and the difference in clinical characteristics, as well as to the efficacy of the medication in controlling medical symptoms.

Our study also indicated that medication adherence was inversely correlated with seizure severity. However, this finding could have been confounded by several clinical and demographic characteristics of the participants. Therefore, we adjusted our analyses for confounders such as age, sex, marital status, educational years, employment status, income level, epilepsy type, and duration of the disease. Interestingly, we observed that seizure severity and serum drug level were both independently related to medication adherence even after adjusting for those confounders. Therefore, our findings show that seizure severity and serum AED level are strong predictors of medication adherence in patients with epilepsy.

In this study, we evaluated the association between medication adherence, seizure severity and serum AED level of the patients with their QoL. In particular, we found that, after controlling clinical and demographic characteristics, medication adherence was directly associated with the overall score of QoL and all its domains, while seizure severity and serum AED level did not have a significant correlation with the QoL. Serum AED levels are not necessarily associated with QoL in patients with epilepsy. That being said it does not provide detailed information on patients' level of adherence over time. Moreover, serum AED levels can only be assessed in patients who are taking second generation AEDs [40]. Moreover, the interpretation of serum AED level depends on the time of sampling and the duration of AED therapy. These problems limit the usefulness of the information regarding serum AED levels in everyday clinical practice.

Although our findings did not confirm a significant correlation between seizure severity and QoL, several studies have confirmed an inverse relationship between seizure severity and QoL in epileptic patients. For example, Harden et al. [41] examined a group of women aged 18-45 with refractory epilepsy and found that, even when controlling for depression, seizure severity was inversely correlated with multiple domains of QoL. Bautista et al. [42] indicated that quality of life for patients with epilepsy was adversely affected by seizure severity. Furthermore, Sancho et al. [43] indicated that QoL in patients with severe seizures has been consistently shown to be worse than for those with mild or moderate seizures.

Moreover, our study indicated that medication adherence was positively correlated with QoL. Indeed, AED non-adherence impacted negatively on QoL as a result of poor seizure control. A number of studies have examined the relationship between medication adherence and QoL. However, the findings remain controversial. Consistent with our findings, several studies have previously demonstrated the beneficial effects of medication adherence on improved QoL in epileptic patients [10, 44, 45] and other diseases [46, 47]. Loon et al. [47] found that adherence to glaucoma medications was associated with better QoL. Moreover, medication adherence has been reported to be associated with increased QoL in patients with epilepsy [44, 45]. However, Martinez et al. [48] could not find any significant association between medication adherence and QoL in patients with type 2 diabetes. In the study by Saleem et al. [21], no relationship was found between medication adherence and QoL in hypertensive patients. However, due to the conflicting results, it remains unclear whether increased seizure severity or decreased QoL is the primary event.

Despite the evidence that medication adherence can improve QoL, it is uncertain whether seizure severity and serum AED level can be replaced by medication adherence to predict QoL. Our hypothesis was that medication adherence may mediate the correlation between seizure severity and QoL, as well as serum AED level and QoL. Using the Sobel test to test our hypothesis revealed that medication adherence did mediate the correlation between seizure severity and QoL. This indicates that less severe seizures may be due to increased medication adherence and eventually lead to increased QoL. Moreover, the Sobel test revealed the mediatory effect of medication adherence on AED level and QoL, suggesting that a higher AED level can be due to increased medication adherence resulting in improved QoL. In addition, these results were supported by the SEM model, which confirmed the proxy effect of medication adherence on the latent score of QoL.

This study revealed that neither seizure severity nor serum AED level had a direct effect on the QoL, although there was an indirect effect between these variables via medication adherence. Therefore, medication adherence is very important to improve QoL in elderly patients with epilepsy, and it should be strongly encouraged by physicians.

According to our findings, elderly people with epilepsy who are concerned about the impact of epilepsy on their independence and QoL could potentially control their seizure symptoms through medication adherence. Furthermore, there is a need to pay more attention to medication management and adherence to improve QoL among the elderly with epilepsy. As the elderly are prone to multiple comorbidities, they are at higher risk of polypharmacy, and therefore may present with a higher risk of non-adherence to medication compared to the younger population. This results in decreased therapeutic benefits for the patient, and increased healthcare expenditure.

There are several strengths of our study, including serum AED level measurement to assess medication adherence,

a relatively large sample size, and longitudinal design, which can help yield firm conclusions. However, some caution is necessary in the interpretation of our findings. Firstly, it is likely that the associations between the variables may also be partially explained by other confounders that were not controlled for in this study, e.g. unhealthy lifestyle. Secondly, we did not assess serum AED level and the QoL at the beginning of the study. Therefore, we are unable to discuss the association between the changes of medical adherence and quality of life throughout the study. Finally, major cognitive and acute psychiatric disorders such as depression and anxiety, which could be key factors affecting both medication adherence and QoL, were excluded from the current study.

Conclusion

In elderly patients with epilepsy, medication adherence significantly correlates with QoL. Given proper medication management, the QoL of these patients can be improved. Therefore, healthcare providers need to provide an appropriate level of support by frequently reviewing drug management and monitoring adherence in elderly patients with epilepsy.

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Early predictors of injectable disease modifying drugs suboptimal response based on clinical and radiological data assessment in Polish Multiple Sclerosis patients

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ABSTRACT

Background. Prospective database studies can provide useful information regarding 'real-world' outcomes and drug efficacy.

Objective. To determine the early predictors of suboptimal treatment responses at two and three years under injectable Disease Modifying Therapy (DMT).

Methods. This was a multi-centre prospective database study. Adult patients who started injectable DMTs between January 2008 and June 2013 were included. The follow-up continued until July 2014. Suboptimal treatment responses were defined as: the presence of clinical relapse and/or Expanded Disability Status Score (EDSS) progression and/or newly emerging T2 lesions or/and gadolinium enhancing lesions on magnetic resonance imaging (MRI). The parameters were assessed up to 24 months prior to, and every 12 months during, the treatment.

Results. Analysis included 297 MS (multiple sclerosis) patients followed for a mean time of 2.3 ± 1.3 years (range 1–5). Within the three years of observation, the persistence and efficacy with injectable DMTs was high. With increased disability, defined by EDSS ≥ 3, the risk of treatment failure increased up to seven times, OR 7.33 in the second year radiological analysis (CI 95% : 1.69–29.2) $p < 0.01$, similar to over two times in the second year clinical analysis, with the baseline symptomatic hemiparesis OR 2.75 (CI 95% : 1.06–7.06) p 0.034. A high relapse rate one year prior to treatment adversely influenced the treatment success at three years, OR 3.04 (CI 95% : 1.49–8.43) $p < 0.01$.

Conclusions . Injectable DMTs should not be chosen for treatment initiation in motoric disabled patients (EDSS ≥ 3) with a high grade of clinical activity. These drugs are effective in less active relapsing-remitting (RR) MS patients.

Key words: multiple sclerosis, disease modifying treatment, annualised relapse rate, Expanded Disability Status Score, magnetic resonance imaging, RIO score, efficacy
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Introduction

Multiple sclerosis (MS) is a chronic demyelinating disease with increasing prevalence in Poland [1]. The course of the disease and its associated rate of disability progression are highly unpredictable and constitute the most common primary neurological cause of disability in young adults [2]. The continued development of diagnostic criteria and increased awareness of typical clinical features have allowed shortening of the diagnosis delay and an earlier

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initiation of treatment [3]. An analysis of the disease onset symptoms and initial relapse rate can help to estimate the most probable course of the disease, with specification as to its aggressiveness [4]. However, the question as to which drug should be chosen for the treatment is still unresolved. The country-wide standardised inclusion and reassessment criteria allowed us to make joint analyses of patients from different centres at a time when only injectable disease modifying treatments (DMT) were available in Poland. First line injectable treatment options included different formulations of interferon beta (INT-β): subcutaneous IFN-β-1b, IFN-β-1a and intramuscular IFN-β-1a or subcutaneous glatiramer acetate (GA). These are well established safety immunomodulatory drugs with all-over efficacy defined in randomised trials at about 30% [5–8]. This includes a moderate influence on lowering the relapse rate and on the clinical and radiological progression of disability. At a time when there are a growing number of newly available treatment options, it is still important to analyse previously used algorithms, either to reestablish them or to ensure correct treatment decisions [9].

Material and methods

Patients

The research design was a multi-centre prospective database study. Four medical centres (Bydgoszcz, Szczecin, Białystok, Zabrze) providing immunomodulatory treatment of MS within the nationally funded treatment programme participated in the research.

Inclusion criteria: adult (over 18 years old) patients with relapsing-remitting (RR) MS who started an injectable DMT between January 2008 and June 2013 were included in this study. The follow-up continued to July 2014. All participants met the 2005 McDonald criteria for MS and had either two relapses or one relapse and a chronologically (three months) separate gadolinium enhancing lesion on magnetic resonance imaging (MRI), within the immediate two year period preceding the start of DMT [3]. We included either patients with a newly confirmed diagnosis or untreated for at least the last six months with a new exacerbation and an Expanded Disability Status Score (EDSS) of up to 4.5. During the time of data collection (between 2008 and 2011), the treatment duration regime in Poland was limited to three years. Some active patients could be recruited several times, always after a new instance of disease exacerbation. Treatment selection for IFN β or GA was based on national eligibility criteria. Patients with Clinical Isolated Syndrome (CIS) or progressive forms of MS were not eligible for this study.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; we have followed uniform requirements for manuscripts submitted to biomedical journals.

Cohorts

The time of treatment initiation and a follow-up period of a minimum of two years allowed us to make a comparative observation of two cohorts. Cohort A comprised patients included from January 2008 up to May 2012, eligible after at least two relapses during the last 24 months before qualification to the treatment. Cohort B comprised patients included from June 2012, eligible after at least one relapse during the last 12 months before qualification to the treatment.

Method

Patient data was collected in an electronic case report form. Clinical and demographic parameters were analysed. The disease activity was determined by the annualised relapse rate (ARR) defined as: MS-related hospitalisation, MS-related Emergency Room visit or MS-related outpatient visit with corticosteroid prescription ± 7 days within one year. EDSS scoring was performed every three months during the treatment by trained staff [10]. Clinical neurological progression was defined as a change of EDSS score of more than 1.0 that was persistent for longer than three months despite a lack of relapse. Magnetic resonance imaging (MRI) was performed at the beginning and after each year of treatment, and was focused on detecting new emerging T2 lesions or/and a gadolinium (GD) enhancing lesion.

Outcomes were defined on the basis of the RIO score:

Optimal clinical response is described as no relapses, no progression in disability (defined as stable EDSS or with a change of less than 1.0) within a year. Optimal radiological response is defined as no changes in NMR (no gadolinium enhancing lesion and less than two T2 lesions). The definition is similar to a RIO score of zero. Suboptimal clinical response is described as one or more relapse and/or progression in disability (defined as increase of EDSS ≥ 1.0) and/or suboptimal radiological response, defined as > 1 active gadolinium enhancing lesion and/or > 2 T2 lesions in a year. This definition is similar to a RIO score of 1 or more [11].

Statistics

Statistical analysis was performed using R (The R Project for Statistical Computing)-R version 3.4.2. In descriptive statistics, the following tests were used: Fisher's exact test to establish differences in proportions, T-test to establish differences in quantitative data (for normally distributed data), Wilcoxon test to establish differences in quantitative data (for non-normally distributed data), Anderson-Darling test to establish the normality of given quantitative data. In order to

determine the influence of main neurological rates (symptoms on MS onset, EDSS) on drugs suboptimal response, univariable logistic regressions were performed.

Results

Two hundred and ninety seven MS patients met the inclusion criteria. The female to male ratio was 2.3:1. The average age of the patients was 35.37 ± 9.92 years (range 18–64 years), and the patients showed mild disability characterised by a mean baseline EDSS of 1.95 ± 1.05. The average treatment delay was 4.12 ± 4.81 years (range 0–24 years). The two studied cohorts were comparable without significant differences on baseline, except for the fact that the more recently included patients (Cohort B) were older, more disabled and more active in their disease course (p 0.01). In both cohorts, the proportion between the newly diagnosed-naïve and previously treated patients was similar (Tab. 1).

Clinical outcome with injectable DMT

Over 85% of patients were under INF β treatment with a mean follow-up time of 2.3 ± 1.3 years (range 1–5). After three years of treatment, no relapses and stable EDSS was observed in 91 patients (85%) which constitutes about one third of the baseline population. The patient loss in follow-up was mainly due to a treatment time limited to three years, established by the nationally funded treatment programme. The evidence of suboptimal treatment response defined as evidence of clinical and/or radiological activity, was stable in the follow up-period, within the range of 15–18%. The reason for stopping or switching the initial DMT therapy was mainly driven by the instability of the clinical course. The mean EDSS score was stable over three years of treatment at about 2.0; we also observed a significant and stable reduction of ARR and GD enhancement $p < 0.01$ (Tab. 2).

Main predictors of suboptimal response to injectable DMT in three years follow-up

Suboptimal clinical response, defined as a RIO score ≥ 1, was further analysed in two separate categories: clinical and radiological response. In univariable logistic regression, the factors predicting worse response to injectable DMTs were comparable in the whole three years of the follow-up period. The main predictor of inefficacy in the first and second years of treatment was the baseline clinical status. With an increase in disability defined as baseline EDSS ≥ 3, the risk of treatment failure increased to over seven times (in the second year radiological analysis), similar to over two times with baseline symptomatic hemiparesis, which in fact influences the EDSS

Table 1. Socio-demographic and clinical characteristics of MS patients at baseline

Variable	Overall (297)	Cohort A (n = 150)	Cohort B (n = 147)	p value
Age (years) mean (SD)	35.37 (9.92)	33.86 (9.42)	36.92 (10.2)	0.01**
Gender (female/male), n	206/91	100/50	106/41	0.38
Age at diagnosis (years) mean (SD)	31.26 (10.12)	29.94 (9.38)	32.60 (10.69)	0.06
Treatment delay (years) mean (SD) range	4.12 (4.81)	3.92 (4.64)	4.32 (4.98)	0.8
	(0–24)	(0–23)	(0–24)	
Previous DMT treatment (No/Yes), n	212/85	107/43	105/42	1.0
BL treatment INF/GA, n	253/44	133/17	120/27	0.1
Onset symptoms: n/%				
Optic neuritis: n/%	99/33.4	52/33.8	47/31.5	0.71
Hemiparesis: n/%	77/25.9	42/28.0	35/24.2	0.43
Cerebellar syndrome: n/%	35/11.8	19/12.6	17/11.6	1.0
Brainstem syndrome: n/%	31/10.4	16/10.6	15/10.2	1.0
Other: n/%	55/18.5	21/14.0	33/22.5	0.2
EDSS on BL mean (SD)	1.95 (1.05)	1.75 (0.97)	2.15 (1.10)	0.01*
EDSS ≥ 3 on BL n/%	44/14.81	16/10.66	28/19.04	0.05*
NMR GD enhancement on BL	62/297	18/132	44/103	< 0.01**
ARR 2 years before BL (SD)	1.535 (0.95)	1.37 (0.86)	1.70 (0.96)	0.01*
ARR 1 year before BL (SD)	1.18 (0.78)	1.0 (0.68)	1.36 (0.89)	0.01*
ARR 6 months before BL (SD)	0.89 (0.68)	0.71 (0.56)	1.07 (0.81)	0.01*

p value represents the statistical difference between the two cohorts; *Wilcoxon test ; **Fisher test; ARR — annual relapse rate; BL — baseline; DMT — disease modifying therapy; EDSS — Expanded Disability Status Score; MRI — magnetic resonance imaging; SD — standard deviation

Table 2. Clinical characteristics of MS patients during treatment

Variable	BL	I year	II year	III year	p value
Overall patients, n	297	297	167	107	-
EDSS mean (SD)	1.95 (1.05)	1.96 (1.12)	1.96 (1.12)	2.018	0.84
ARR (SD)	1.53 (0.95)	0.13 (0.41)	0.13 (0.41)	0.13 (0.41)	< 0.01
NMR GD enhancement mean (SD)	0.54 (1.42)	0.06 (0.32)	0.06 (0.32)	0.06 (0.32)	< 0.01
Continued treatment n/%	-	283/95.0	161/96.4	104/97.2	0.43
Optimal clinical/radiological response (RIO 0) n/%	-	244/82.2	142/85.0	91/85.0	0.52
Suboptimal clinical/radiological response (RIO ≥ 1) n/%	-	53/17.8	25/15.0	16/15.0	0.51

p value represents the statistical difference between the analysed groups; ARR — Annual Relapse Rate; BL — baseline; EDSS — Expanded Disability Status Score; GD — gadolinium; SD — standard deviation

Table 3. Main predictors of suboptimal response to injectable DMT in three years follow-up: univariable logistic regression

Suboptimal response	Variable	OR	CI 95%	p-value
First year clinical	EDSS on BL	1.38	1.00–1.891	0.048
	Hemiparesis on BL	2.17	1.04–4.406	0.034
First year radiological	EDSS on BL	0.55	0.311–0.904	0.026
	Age at treatment initiation	0.93	0.88–0.98	0.02
Second year clinical	Hemiparesis on BL	2.75	1.065–7.066	0.034
Second year radiological	EDSS on BL	2.13	1.143–4.072	0.018
	EDSS on BL ≥ 3	7.33	1.69–29.206	< 0.01
Third year clinical	ARR one year prior to treatment	3.047	1.322–7.71	0.01
Third year radiological	ARR one year prior to treatment	3.667	1.325–12.636	0.029

ARR — Annual Relapse Rate; BL — baseline; EDSS — Expanded Disability Status Score

score. The younger age and lower EDSS on treatment initiation positively influenced optimal radiological response in the first year. With longer treatment duration, the ARR one year before the treatment initiation seems to play a negative role. With a higher relapse rate, the suboptimal response risk increased three times in the third year of treatment. No other demographic or clinical factors played a role in predicting a worse outcome (Tab. 3).

Discussion

Open compartmental studies concerning first-line RRMS treatment have shown a significant reduction of disease activity. In the first two years of INF B treatment, the ongoing disease activity has been reported as between 16% and 29% [12–16]. Freedom from disease activity has become a widely proposed system of optimal clinical outcomes analysis based on relapse rate, EDSS and radiological signs of new active lesions. The often used RIO score can be translated to NEDA showing an optimal disease control in a similar way [16–18]. In this multi-centre prospective database study, we showed a high efficacy of injectable first-line DMTs. This was achieved by a good clinical response in lowering the BL rate of ARR from 1.3 to 0.13 (after one and two and three years of treatment). EDSS stabilization, together with the reduction of radiological progression, resulted in good disease control in over 80% of patients.

Some other studies, in so far as our results, show high efficacy of first-line injectable medications in the treatment of RRMS patients [18–23]. In the study by Sorenson et al., based on the Danish Nationwide Database containing health records from RRMS patients, there was no clear difference in the efficacy of immunomodulatory treatment with injectable DMTs [22, 24–25].

We based the comparison of the optimal and suboptimal treatment responses on the RIO score. To analyse the predictors for suboptimal response, we concentrated mainly on baseline variables that could lead to treatment failure. Baseline EDSS ≥ 3 or hemiparesis as the initial MS manifestation increases such a risk more than two times. A similar conclusion without any specific cut-off was described in an 18 year-long observational cohort study of treatment-naïve patients from Canada [19]. Also in other reports, high EDSS score has been considered to be the main factor predicting interruption of

therapy, which in fact is similar to a suboptimal treatment response [26–27]. Due to the therapy outcome optimisation, it is recommended attention be paid to more active/progressive patients at diagnosis [4]. Those patients with higher levels of disability in the early relapsing-remitting course of the disease should be considered as highly active, with an indication for therapeutic decisions other than first line DMTs [9]. The same is true for relapse active patients before the treatment, as relapses are the clinical manifestation of inflammation. In our cohort, the risk of being suboptimal responders at three years was more than three times higher for relapse active patients one year before treatment.

Another important aspect that we took into consideration was treatment efficacy estimation by early and late therapy initiation. We could compare the outcomes form treatment-naive and retreated patients. This observation was possible because of country-specific regulation on the time of data collection. According to the previously used (from 2008 to 2012) guidance, the nationally funded treatment programme was limited to three years. Some active patients could be recruited several times, always after a new exacerbation of the disease. The average treatment delay in our study was four years. Only 28% (85) of patients were treated within > 12 months after diagnosis as treatment-naïve. Nearly 27% started the treatment later than five years, and 11% later than 10 years, after diagnosis. Despite not proven worsening of efficacy, treatment delay in our study was twice as long as that observed in a comparable time frame in Spain [28]. Taking into consideration the differences between treatment-naïve and retreated patients, we could only confirm a worse outcome in patients with profound clinical disability on treatment initiation, without differences between these two groups.

In previous Polish analysis, immunomodulatory drugs were used in only 24% of patients: mainly INF β (81%) and GA (13%) [29]. This time, the analysis showed a similar proportion and consistent INF β dominance, in contrast to other countries [19]. In a similar observation period in the US, nearly 40% of newly-diagnosed MS patients were on treatment [30]. This shows that the problem with treatment initiation is not only related to country-specific regulations or budget, but also to patients' and physicians' beliefs in its efficacy and safety.

In a long term observation of injectable DMTs, the stop/switch rates were mainly dependent on treatment duration, with intolerance as the primary reason for stopping, followed by inefficacy [19, 31–37]. Persistence in specific therapy indirectly describes the treatment efficacy. In our study, the efficacy was over 80% but the persistence was influenced rather by no other treatment options at that time.

Our study had some methodological shortcomings due to its multi-centre nature. Follow-up MRI scans were performed and analysed in different locations, albeit under one assessment protocol [38]. The same is true for EDSS scoring. An average treatment delay estimated as almost four years after MS diagnosis is another limitation of our study. However, this reflected the fact that country-specific qualification procedures led to late initiation of the treatment, which is inconsistent with common standards. We could determine the baseline predictive correlations only in univariate logistic regression analysis.

Many novel MS medications have been registered recently [39] and integrated to an improved MS treatment programme in Poland. Confronting the previously used algorithms with well-established outcomes control (RIO score) that we have used so far provides the insight that injectable DMTs are effective in RRMS patients (causing lowering of ARR and disease activity reflected in MRI) with limitation to less active and less clinically well patients. Our findings confirm that a careful baseline variables assessment can be helpful in predicting treatment response in injectable first-line drugs.

Conclusions

Patients with greater disability (EDSS ≥ 3) at treatment initiation or hemiparesis as the initial symptom were more likely to fail at the second year of treatment. A high relapse rate one year prior to treatment adversely influences the treatment success at three years. Our findings confirm that first-line injectable drugs should not be chosen for treatment initiation in motoric disabled patients with a high grade of clinical activity. These drugs are effective in less active MS-RR patients.

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Should non-movement specialists refer patients for SPECT-DaTSCAN?

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Abstract

Background. SPECT with radioligand DaTSCAN (SPECT-DaTSCAN) is a sensitive tool used for assessing the functional integrity of the presynaptic part of the nigrostriatal dopaminergic system. The procedure is useful whenever there is a need to distinguish between neurodegenerative parkinsonism and other parkinsonian syndromes in subjects with equivocal signs and symptoms. It can be assumed that the neurologist's decision to perform SPECT-DaTSCAN depends on his or her experience and skill in the diagnosis of parkinsonian and tremor syndromes.

Aims. To assess the accuracy of referrals to SPECT-DATSCAN made by non-movement disorders specialists.

Material and methods. Sixty seven patients referred for SPECT-DaTSCAN by a general neurologist were studied. In all subjects, a movement disorder specialist performed the neurological examination, collected medical history, and analysed previous treatments and the results of diagnostic tests.

Results. Evaluation carried out by a movement disorder specialist did not confirm an indication for SPECT-DaTSCAN in 31 patients (46.3%). General neurologists needed support for clinical diagnosis with SPECT-DaTSCAN most frequently in subjects with parkinsonism even though they were presenting a full-blown disease manifestation and even though the patients met the diagnostic criteria for Parkinson's disease or one of the atypical parkinsonian syndromes.

Conclusions. Our presented results probably reflect the limited experience of general neurologists in the evaluation of parkinsonian syndromes and tremor. The use of SPECT-DaTSCAN by non-movement disorders specialists is associated with a significant risk of overuse of this tool. To minimise this risk, the skills of general neurologists in diagnosing parkinsonian and tremor syndromes should be improved. Moreover, patients should be provided with access to movement disorders specialists.

Key words: SPECT-DaTSCAN, referrals, non-movement disorders specialists, movement disorders specialists
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Introduction

^{123}[I]ioflupane ([^{123}I]-fluoropropyl CIT, ^{123}I-FP-CIT, DaTSCAN®, GE Healthcare) is a dopamine transporter (DAT) radioligand for single-photon emission tomography (SPECT). Degeneration of dopaminergic neurons in the substantia nigra results in reduced DAT concentration within the striatum, and therefore SPECT-DaTSCAN is used as a marker of the integrity of the presynaptic part of the nigrostriatal dopaminergic system [1–7].

DaTSCAN was approved by EMA in Europe in 2000 and by FDA in the USA in 2011 for the differential diagnosis of parkinsonian tremor and essential tremor (ET) and of Alzheimer's disease (AD) and diffuse Lewy body disease (LBD) [8–10]. In clinical practice, SPECT-DaTSCAN has wider applications in that it allows for differential diagnosis between

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neurodegenerative parkinsonisms on the one hand, and parkinsonian syndromes without the presynaptic involvement of the nigrostriatal dopaminergic system on the other hand.

It can be assumed that the neurologist's decision to perform SPECT-DaTSCAN depends both on his or her experience and skill in the diagnosis of parkinsonian syndromes as well as on his or her knowledge of the usefulness and limitations of this technique. The aim of our paper was to assess the accuracy of referrals to SPECT-DATSCAN made by non-movement disorders specialists.

Material and methods

At the Department of Nuclear Medicine, we introduced a routine procedure according to which the indications for all patients referred for SPECT-DaTSCAN were verified by one of two neurologists (AG or AB) with more than 15 years of experience in Parkinson's disease and other movement disorders (> 50 patients seen per month). In all subjects, a neurological examination was performed, a medical history was carefully collected, and previous treatments and the available results of diagnostic tests were analysed.

Consecutive patients referred by a general neurologist from July 2016 to December 2017 were included in this present analysis.

The results presented in this paper are a retrospective analysis of data from routine practice and so there was no need to apply for the approval of the Bioethical Committee.

Results

Sixty seven patients referred for SPECT-DaTSCAN by a general neurologist were studied. Evaluation carried out by a movement disorder specialist did not confirm the indications for dopaminergic functional imaging in 31 patients (Group A), but found it to be reasonable in the other 36 subjects (Group B).

Group A. Patients with unconfirmed indications for SPECT-DaTSCAN study

In this group of 31 patients (Tab. 1), the largest subgroup consisted of 22 patients (age 52–91 years, disease duration 1–16 years) who were referred for SPECT-DaTSCAN with an indication formulated by a general neurologist as „suspicion of PD". In the opinion of a movement disorder specialist, the observed clinical symptoms were fully sufficient to diagnose PD in 12 subjects (aged 52–84, disease duration 1–5 years). All of them met the UK Brain Bank main diagnostic criteria for PD [12]: bradykinesia plus one or more of rigidity, tremor, or postural instability. Moreover, nine of these 12 (age 52–84 years, symptoms duration 2–5 years) presented with between one and four of the supportive prospective positive criteria [12]: unilateral onset, rest tremor, progressive disorder, persistent asymmetry affecting the side of greatest onset, excellent (70–100%) response to levodopa, and 1–4 years duration of illness.

Table 1. Group A. Patients with unconfirmed indication for SPECT-DaTSCAN study

Diagnosis or reason for referral for SPECT-DaTSCAN provided by the referring neurologist	Suspicion of Parkinson's disease or other parkinsonism						Tremor		Differential diagnosis: Parkinson's disease vs psychogenic parkinsonism	Other
Diagnosis made by movement disorder specialist (number of patients)	Parkinson's disease (12)	Essential tremor or essential tremor plus (5)	Multiple system atrophy (2)	Cortico-basal syndrome (1)	Progressive supranuclear palsy (1)	Depression (1)	Dystonic tremor (2)	Essential tremor plus (2)	Parkinson's disease (3)	Psychogenic symptoms without parkinsonism (1)	MRI scan suggesting angioma within lenticular nucleus in patient with vertigo; no signs of parkinsonism (1)

ET [13] was diagnosed in three patients (two female and one male, 58–70 years) with 3–6 years history of symmetrical bilateral upper limb action and postural tremor. All these patients had also developed head tremor, but no signs of parkinsonism were observed. In two male subjects without parkinsonian signs, a diagnosis of essential tremor plus [13] was made. The first of these, a 78 year-old patient with a 16 years history of tremor, presented also with impaired tandem gait. The second of them, a 91 year-old subject, had suffered from kinetic and postural upper limb symmetric tremor and head "no-no" tremor for six years. Impairment of tandem gait was found, and his mother had also suffered from tremor.

In Group A there were also four patients with unquestionable parkinsonian syndrome and other accompanying signs that allowed us to recognise one of the atypical parkinsonisms.

Two of these subjects met the diagnostic criteria for probable multiple system atrophy (MSA) [14, 15]. A 54 year-old female had a three-year history of progressive, more or less symmetrical, bradykinesia and rigidity which did not respond to levodopa. She presented also with dysarthria, dysphagia, laryngeal stridor, cortical myoclonus of the fingers (polyminimyoclonus), ataxic gait, postural instability, Babinski sign and orthostatic hypotension manifesting with dizziness. In the second patient, a 63 year-old man, bradykinesia, rigidity (right ≥ left) and postural, rest and action tremor (right ≥ left) had progressed for four years, and these symptoms did not respond to levodopa. There was a history of REM behaviour disorder, dysphagia, urinary incontinence, and orthostatic hypotension. He presented moreover with cerebellar dysarthria, laryngeal stridor, tendency for a drooping head, ataxia and Babinski sign.

The next patient in this subgroup, a 67 year-old woman with a four-year disease duration presented with asymmetrical (right ≥ left) rigidity and bradykinesia with dystonic posture and alien limb syndrome on the right, apraxia dysgraphoesthesia of the right upper limb, and mild cognitive impairment. She met the diagnostic criteria of probably corticobasal degeneration syndrome (CBS) [16].

A 68 year-old patient with a four-year history of falling backwards (observed from the first year of the disease), presented with — rather symmetrical — bradykinesia and rigidity, neck stiffness, tendency to retrocollis and vertical gaze palsy. Brain MRI scans showed midbrain atrophy. Probable progressive supranuclear palsy (PSP) — PSP with Richardson's syndrome — was diagnosed according to MDS diagnostic criteria [17].

Finally, there was a 78 year-old woman without any parkinsonian signs with diagnosis of depression made by a psychiatrist.

Among the patients with unconfirmed indications for the SPECT-DaTSCAN study there were seven subjects who were referred by a general neurologist due to tremor.

In two female subjects (age 71 and 62 years, disease duration 15 and 4 years, respectively) dystonic tremor was diagnosed by the movement disorder specialist. In neither of them were there parkinsonian signs, while the examination revealed the presence of mild torticollis and upper limbs dystonia.

The next two females (78 and 68 years, disease duration 7 and 6 years, respectively) presented with slightly asymmetric action tremor of upper limbs, impaired tandem gait and — in the first of them — memory impairment. No parkinsonian signs were present. Essential tremor plus [13] was diagnosed in both these cases.

Two female patients and one male patient (age 51, 55 and 57 years, disease duration 3, 1 and 4 years, respectively) showed a full-blown asymmetric parkinsonian syndrome (including asymmetric rest tremor) which met the core UK Brain Bank criteria for Parkinson's disease. In a male subject with a four-year history of rest tremor, a good response to levodopa had been well documented.

A 39 year-old female (disease duration 1 year) was referred for SPECT-DaTSCAN as part of a differential diagnosis of psychogenic parkinsonism and PD. The patient reported many subjective complaints including pain and numbness located bilaterally within the feet, ankles and knees. Peripheral neuropathy and pathology within the spinal cord had been previously excluded. She did not meet the diagnostic criteria for restless legs syndrome. Her neurological examination was normal and, most of all, there were no parkinsonian signs. In the movement disorder specialist's opinion, the patient's symptoms were of psychogenic origin.

The last patient in Group A, a 61 year-old female, reported vertigo with onset one year ago. Her neurological examination was normal, and brain MRI scans suggested angioma within lenticular nucleus. According to the neurologist referring this subject for SPECT-DaTSCAN, the purpose of the study was „the assessment of dopaminergic system".

In patients with unconfirmed indications for SPECT-DaTSCAN, the study was not performed. The exception was two patients with a diagnosis of atypical parkinsonism made by the movement disorders specialist; in these cases, the SPECT-DaTSCAN result was abnormal.

Group B. Patients with confirmed indications for SPECT-DaTSCAN

In the opinion of movement disorder specialists, the decision to perform the SPECT-DaTSCAN study was well-founded in 17 female and 18 male subjects (Tab. 2).

In 16 patients (nine women and seven men, age range 37–57 years; disease duration 1–4 years), the imaging study was a part of the process of differential diagnosis between essential tremor and PD. At this point, in all these cases, it was indeed difficult or impossible to make a diagnosis solely on the basis of clinical symptoms.

The next subgroup consisted of four male patients (age range 61–77, disease duration 2–6 years), who required differential diagnosis between vascular and neurodegenerative parkinsonism, especially PD.

Table 2. Group B. Patients with confirmed indications for SPECT-DaTSCAN study

Diagnosis or reason for referral forSPECT-DaTSCAN provided by the referring neurologist (number of patients)	Parkinson's disease (9) Parkinson's disease ***vs*** essential tremor (3) Upper limbs tremor (2) Right hand tremor (1) Right limbs tremor (1)	Suspected Parkinson's disease (4)	Suspected parkinsonism (4)	Suspected parkinsonism (5)	Suspected parkinsonism (2)	Suspected parkinsonism (1)	Upper limbs tremor, suspected Parkinson's disease (1)	Dystonia-parkinsonism syndrome *vs* neurodegenerative parkinsonism (1)		Suspected Parkinson's disease (1)
Diagnosis or reason for referral for SPECT-DaTSCAN according to movement disorder specialist	Differential diagnosis: Parkinson's disease *vs* essential tremor	Differential diagnosis: neurodegenerative parkinsonism *vs* vascular parkinsonism	Suspected early Parkinson's disease (UK Brain Bank criteria not met)	Clinically Uncertain Parkinsonian Syndrome	Suspected Multiple System Atrophy	Suspected Progressive Supranuclear Palsy	Neuropathic tremor *vs* neurodegenerative parkinsonism	Dystonia-parkinsonism syndrome *vs* neurodegenerative parkinsonism		Neurodegenerative parkinsonism *vs* drug-induced parkinsonism

Three men and one woman (aged 37–51 years, disease duration 1–2 years) suspected by the referring neurologist for Parkinson's disease, presented with different combinations of two core UK Brain Bank criteria parkinsonian signs, but they did not meet the diagnosis of PD.

Furthermore, five patients (three females and two males, age 58–67, disease duration 3–7 years) were classified as Clinically Uncertain Parkinsonian Syndrome (CUPS). They did not meet the diagnostic criteria for PD or any atypical parkinsonism, and there was a poor response to levodopa, so drug-induced parkinsonism was excluded.

Two patients (a 41 year-old female and a 37 year-old male, both with three years of symptoms duration) with uncertain symptoms suggesting MSA and a man (62 years, disease duration 2 years) presenting with scant symptoms and suspected of PSP were also qualified for SPECT-DaTSCAN to support the pre-scan diagnosis.

The need to perform the SPECT study was confirmed also in a 69 year-old woman (symptoms duration 2 years) with axonal polyneuropathy and asymmetric (L > P) postural, rest and action tremor. The aim was to confirm or to exclude the co-occurrence of neurodegenerative parkinsonism.

In another 39 year-old female patient, writer's cramp had developed when she was about 20 and subsequently dystonia spread to the contralateral upper limb. Neurological examination revealed unilateral bradykinesia and rigidity. Neither dystonia nor parkinsonian signs responded to levodopa. Differential diagnostics between dystonia-parkinsonism syndrome and neurodegenerative parkinsonism required imaging of the nigrostriatal dopaminergic system.

Finally, we accepted a 59 year-old woman who had been treated with neuroleptics for many years before acute, asymmetric parkinsonism had developed. The purpose of the SPECT study in this case was to exclude the co-existence of nigrostriatal degeneration.

Discussion

The concentration and distribution of DAT within the striatum reflect the number of active dopaminergic neurons in the substantia nigra. SPECT-DaTSCAN is a sensitive tool for assessing the functional integrity of the presynaptic part of the nigrostriatal dopaminergic system [1–7]. DaTSCAN is currently approved in Europe and the USA for use in the differential diagnosis between PD tremor and essential tremor as well as for differentiation between AD and LBD. However, in clinical practice, SPECT-DaTSCAN is used much more widely and may be useful whenever there is a need to distinguish between neurodegenerative parkinsonism (PD, MSA, PSP, CBS) and parkinsonian syndromes not resulting from damage to the dopaminergic system in subjects with equivocal signs and symptoms (DIP, PP, VP) [18].

SPECT-DaTSCAN is a very sensitive functional marker of the lesion of the presynaptic part of the nigrostriatal system

and – according to new MDS diagnostic criteria [19] – normal dopaminergic imaging is an absolute exclusion criterion for PD. SPECT-DaTSCAN is not recommended as a part of routine diagnostic procedure because in patients who meet the UK Brain Bank diagnostic criteria for PD the results of dopaminergic imaging are abnormal [12]. The same applies to atypical parkinsonisms if the main signs of parkinsonian syndrome are present [14–17]. Moreover, SPECT-DaTSCAN is completely useless in the differential diagnosis of neurodegenerative parkinsonisms: PD, MSA, PSP and CBS [20–23].

The usefulness of SPECT-DaTSCAN in the practice of movement disorders centres has been confirmed by numerous reports. At referral movement disorders centres, the diagnosis and treatment were changed in more than half of the patients as a result of dopaminergic imaging [24–25].

SPECT-DaTSCAN is a relatively expensive procedure, and therefore the rational use of this diagnostic tool is of particular importance. The British NICE 2017 [11] guidelines underline that this procedure may eliminate the costs of unnecessary treatment of patients with a false positive diagnosis based on a neurological examination. On the other hand, it has been suggested that SPECT-DaTSCAN should not be used in all subjects suspected of PD, and it is recommended that this procedure "should be available to specialists with expertise in its use and interpretation".

Until 2018, the availability of SPECT-DaTSCAN in Poland was very limited. However, at the Department of Nuclear Medicine in Medical University of Łodź a number of patients could be tested without any payment from their side (the procedure was funded by the Regional Branch of the National Health Fund). Patients could be referred by both movement disorder specialists and neurologists with no special interest in movement disorder (i.e. non-movement disorders specialists, general neurologists).

There are no reference centres for neurological subspecialties within the Polish healthcare system. Patients with Parkinson's disease and other movement disorders are diagnosed and treated by general neurologists who have differing levels of experience in this area and who are usually not able to refer patients to a movement disorders specialist for consultation. There is therefore a risk that the SPECT-DaTSCAN will be overused in this situation.

To the best of our knowledge, this is the first study to have assessed the correctness of non-movement disorders specialists' decision to use SPECT-DaTSCAN in routine clinical practice.

We evaluated 67 patients referred by general neurologists for dopaminergic imaging to the Department of Nuclear Medicine. In 31 (46.3%) of these subjects, in the opinion of movement disorders specialists, it was possible to make a diagnosis without a SPECT study, solely on the basis of neurological examination and data from medical history. Non-movement disorders specialists needed support for clinical diagnosis with SPECT-DaTSCAN most often in cases of parkinsonism. It should be noted that this concerned patients who had been ill for several years and had full-blown disease symptoms. The same problem occurred in subjects with tremor. This, in our opinion, most likely reflects the limited experience of this group of neurologists in the diagnosis of tremor and parkinsonian syndromes.

The general neurologists who referred patients to the Department of Nuclear Medicine were not obliged to provide alternative diagnoses which, according to them, needed differentiation using SPECT-DaTSCAN. Therefore, we could not assess to what extent the choice of SPECT-DaTSCAN as a tool to resolve the neurologist's uncertainty regarding the pre-scan diagnosis considered this technique's basic application, i.e. the distinction between degenerative and non-degenerative parkinsonisms.

In the group of patients with confirmed indications for the SPECT-DaTSCAN study, there were several subjects in whom the signs and symptoms revealed by neurological examination were insufficient to make a diagnosis. In these cases, the abnormal result of imaging could confirm the presence of nigrostriatal degeneration and enable early diagnosis. This was a finely balanced decision, because in these cases longer clinical observation would probably also allow for diagnosis.

The presented results show that the use of SPECT-DaTSCAN by non-movement disorders specialists is associated with a significant risk of overuse of this diagnostic tool. To minimise this risk, general neurologists' skills in diagnosing parkinsonian syndromes should be improved, and at the same time patients should be provided with access to a movement disorders specialist. In addition, broad access to DaTSCAN financed by the National Health Fund should be connected to an educational programme addressed to all neurologists.

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Analysis of echocardiographic parameters of cardiac function in patients with acute stroke

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ABSTRACT

Introduction. Cardiologic diagnostics in stroke patients is designed to identify heart disease as a potential cause of stroke. The aim of this study was to evaluate the effect of low ejection fraction (EF) and left ventricular systolic/diastolic dysfunction (LVSD, LVDD) on the neurological state on the 1st day of stroke, as well as post-stroke functional status at 30 days after stroke.

Patients and methods. For a prospective study, 162 stroke patients (mean age 74 years) were qualified. They were analysed according to neurological state on the 1st day of stroke, the results of transthoracic echocardiography, and functional status at 30 days after stroke.

Results. The neurological state on the 1st day after stroke was significantly worse in patients with LVSD. In patients with reduced EF, functional status was significantly worse at 30 days after stroke. Patients with E/A 0.8–2 had a significantly worse functional status compared to patients with E/A < 0.8. Individuals with E/A 0.8–2 and segmental LVSD or EF < 50% had significantly worse functional status compared to patients without LVSD. An independent factor for moderate/severe status was identified: E/A > 0.8 (RR 3.28 [95% CI 1.15-9.37]); independent factors for poor functional status were lower EF (RR 4.68 [95% CI 1.22–18.00]) and age (RR 4.68 [95% CI 1.22–11.00]).

Conclusions. One quarter of patients in the acute phase of stroke have LVSD and/or LVDD. LVSD adversely affects both neurological status in acute stroke as well as functional status in the short-term follow-up. Age at first-in-life stroke incidence and lower EF are predictors of poor functional status one month after a stroke.

Key words: stroke, cardiac dysfunction, fraction ejection, mRankin
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Introduction

Cardiologic diagnostics in stroke patients is designed to identify the presence of heart disease as a potential cause of acute cerebral ischaemia and to estimate the risk of stroke recurrence, which is high in patients with myocardial contractile dysfunction and/or thrombosis in the cavities of the heart. Although left ventricular dysfunction (LVD) is considered to be an independent risk factor for stroke, the results of several studies have not shown any significant increase in embolic incidence in patients with LVD [1–3]. A possible explanation for the discrepancies in research results is the type of anticoagulant therapy used that modifies the risk of cerebral and/or systemic embolism to varying degrees. The adverse effect of LVD on the status of patients with chronic stroke has been reported. However, the importance of LVD for neurological status in the early period of stroke onset has not been clearly established. Given the haemodynamic effects of LVD in the cerebral circulation, the effect of worsening hypoperfusion in the ischaemic zone is to be expected.

The aim of this study was to evaluate the potential effect of low ejection fraction (EF), and segmental systolic dysfunction and left ventricular diastolic dysfunction, on the neurological state of patients on the 1st day after stroke onset, as well

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as post-stroke functional status at 30 days after stroke. An additional objective was to evaluate the significance of other cardiac echocardiographic parameters in acute stroke and the short-term prognosis in this group of patients.

Methods

For a prospective study covering the period 2015–2016 in the Neurology Department, 162 patients (77 women, 85 men), mean age 74 years (71.9 ± 12.6) [25–96] were classified, with the first clinically manifested stroke identified according to the WHO clinical criteria and visible in neuroimaging (computed tomography and/or magnetic resonance imaging of the head) acute ischaemic lesion of the brain [1]. Other main inclusion criteria were: time from onset of stroke symptoms to hospital admission ≤ 24 hours; and the pre-stroke status according to the modified Rankin Scale (mRS) ≤ 1 point.

All patients included in the study were analysed according to:

- age when they had their first-in-life stroke
- presence of comorbidities such as atrial fibrillation (AF), arterial hypertension (AH), coronary heart disease (CHD), diabetes mellitus (DM) and lipid disorders (LD), > 70% atherosclerotic carotid stenosis (ipsilaterally to the ischaemic brain lesion)
- neurological state on the 1st day after stroke onset evaluated according to NIHSS (National Institute of Health Stroke Scale) [3]
- anatomic location of stroke (total anterior cerebral infarct, TACI); partial anterior CI (PACI), lacunar CI (LACI), and posterior CI (POCI)
- early therapeutic management in the acute stage of stroke (thrombolytic intravenous (rtPA iv), endovascular thrombectomy, antiplatelet treatment)
- the results of transthoracic echocardiography (TTE) within the first two days of stroke onset, including heart cavity dimensions, left ventricular contractility and valvular function evaluated according to the recommendations of the European Association of Cardiovascular Imaging (EACVI)
- functional status at 30 days after stroke according to the mRS scale (based on information obtained from the patient and/or carer during a phone call [4].

Diagnosis of AH was consistent with the recommendations of the European Society of Cardiology (ESC), DM was diagnosed according to the criteria of the Diabetes Association, dyslipidaemia was defined according to the ESC recommendations (Guidelines for the Management of Dyslipidaemias) [4–6].

The degree of stenosis of common carotid artery and/or internal carotid artery was assessed according to the NASCET criteria [7]. The TTE was performed using the Philips Epiq 7.

The patients were divided into groups depending on the presence of segmental contractility abnormalities (patients with present *vs* absent contractility dysfunction), ejection fraction (EF < 50% *vs* ≥ 50%), left atrial size (LA ≤ 40 mm *vs* > 40 mm), left ventricular end-diastolic dimension (EDD < 56 mm *vs* ≥ 56 mm), mitral regurgitation degree (MR 1 + 2 *vs* 3), aortic stenosis degree (AS 1 + 2 *vs* 3), aortic regurgitation degree (AR 1 + 2 *vs* 3), relative wall thickness (patients with present *vs* absent hypertrophy) or eccentric hypertrophy (patients with present *vs* absent eccentric hypertrophy). In these groups, mean scores for NIHSS (neurological state on the 1st day after stroke onset) and mRS (functional status at 30 days after stroke onset) were calculated, and a comparison was made between subgroups. Next, 113 patients without atrial fibrillation were divided into three groups depending on the rate of mitral inflow E to A: group A: E/A ratio ≤ 0.8 - patients with impaired LV relaxation; group B, which included patients with no abnormalities or with pseudo-normal pattern of mitral inflow: E/A 0.8-2; and group C - patients with restricted mitral inflow pattern: E/A > 2. In these groups, mean scores for NIHSS were calculated (on the 1st day after stroke), and mRS (at 30 days after stroke), and a comparison was made between the groups.

For the identification of patients with left ventricular diastolic dysfunction with pseudo-normal pattern of mitral inflow, patients in group B were divided into two subgroups according to the following criteria: B1 — patients with E/A ratio 0.8–2, present segmental contractility dysfunction and/or EF < 50%; subgroup B2 — patients with E/A 0.8–2, absence of segmental contractility dysfunction and normal EF (> 50%). Neurological status according to NIHSS (24h after stroke onset), and functional status according to mRS (30 days after stroke onset) were assessed in subgroups B1 and B2 and the mean values obtained were compared. Multi-factorial analysis was performed to determine independent factors of bad neurological status on the 1st day (NIHSS > 10 points) and poor prognosis defined as the patient receiving 3–6 points on mRankin Scale at 30 days after stroke. The following parameters were included in the analysis: age, sex, arterial hypertension, diabetes mellitus, coronary heart disease, atrial fibrillation, lipid abnormalities, > 70% carotid stenosis, location of stroke (PACI, TACI, POCI, LACI), therapeutic management in the acute stage of stroke (reperfusion therapy- rtPA or/and thrombectomy, antiplatelet therapy without reperfusion strategies), EF reduction, size of LA, AS, MR, RWT, EDD, and NIHSS 24h after stroke for the identification of prognostic factors for one month after the onset of stroke.

All statistical analyses were performed using STATISTICA 8.0 PL software. Chi-square and Student's tests were used for categorical variables. The Mann-Whitney U test was used to compare the study groups and subgroups for the nonparametric distribution of some of the parameters. Finally, an analysis was made using a single and multi-factorial method of nonlinear estimation — logistic regression (STATISTICA 5.0PL) — to identify independent factors for moderate/severe neurological state and post-stroke disability at 30 days after stroke. $P < 0.05$ was considered statistically significant.

Ethical approval was not necessary for preparation of this article.

Results

The baseline characteristics of patients enrolled in the study are presented in Table 1.

The neurological state on the 1st day after stroke was significantly worse in patients with left ventricular contractile dysfunction. In patients with reduced ejection fraction assessed within the first two days after stroke functional status at 30 days after stroke was significantly worse. In patients with left ventricular hypertrophy and/or left atrial enlargement, both neurological and functional status was worse, but the differences relative to patients with normal LV and LA were not statistically significant (Tab. 2).

Patients with E/A ratio 0.8–2 had a significantly worse functional status after one month of stroke onset compared to patients with E/A < 0.8 (Tab. 3).

Patients with E/A 0.8–2 and LV contractile dysfunction LVSD and/or EF < 50% had significantly worse outcomes in functional status assessment compared to patients without LV systolic dysfunction (Tab. 4).

In multi-factorial analysis, only one independent factor — E/A > 0.8 (RR 3.28 [95% CI 1.15–9.37] p < 0.0208) was identified for moderate/severe neurological status (NIHSS > 10 points) on the 1st day of stroke. There were two independent factors for poor functional status prognosis (3–6 mRankin) at 30 days after stroke: lower EF (RR 4.68 [95% CI 1.22–18.00], p 0.0186) and age RR 4.68 [95% CI 1.22–11.00], p < 0.0179. The other analysed clinical and echocardiographic parameters were not independent factors for patients' state.

Table 1. Characteristics of the patients

Parameter	Group n = 162
Age	71.9 ± 12.6 [25–96] median 74
Sex F/M	77/85
DM	46 (28.4%)
AH	143 (88.3%)
AF	49 (30.2%)
AF *de novo*	14 (8.6%)
MI	28 (17.3%)
Location of stroke	
TACI	69 (42.6%)
PACI	40 (24.7%)
LACI	44 (27.2%)
POCI	9 (5.6%)
rtPA-therapy	38 (23.6%)
thrombectomy	6 (3.7%)
antiplatelet without reperfusion therapy	117 (72.7%)

F — female, M — male, DM — diabetes mellitus, AH — arterial hypertension, AF — atrial fibrillation, MI — past myocardial infarct, PACI — partial anterior cerebral infarct, TACI — total anterior cerebral infarct, POCI — posterior cerebral infarct, LACI — lacunar cerebral infarct, rtPA — recombined tissue plasminogen activator

Discussion

In the present study, abnormal echocardiographic parameters indicating structural and/or functional myocardial dysfunction were found in 23% of patients. The most important result of the present study is the finding of unfavourable effects of both systolic and diastolic left ventricular dysfunction on the course of stroke. The significance of selected LVD parameters for stroke patient status varies and is marked both on the 1st day after stroke as well as one month after the onset of symptoms. Knowledge of the presence of cardiac dysfunction in a stroke patient is not only important for prognosis but may be crucial for planning early and subsequent rehabilitation.

Population studies estimate the incidence of left ventricular dysfunction to be about 15 –25%, including 0.9–6% of patients who are asymptomatic [8–11]. LVD is more common in people > 65 years of age, and in the subpopulation of patients with arterial hypertension and diabetes [8]. Older age, hypertension and diabetes also increase the risk of stroke. LVD is a consequence of cardiomyocyte death because of oxidative stress originating in the cardiomyocytes as a result of ischaemia, infection, or toxicity [12]. Clinical manifestations of heart failure such as dyspnoea and reduced exercise tolerance are more common in left ventricle diastolic dysfunction (LVDD). This means that many patients may be unaware of their cardiac contractility dysfunctions, and according to the Framingham study the mortality rate of patients with left ventricular systolic dysfunction is higher, and it constitutes 17.9% (compared to 8.9% in patients with diastolic dysfunction, and 3.7% in the control group) [13].

Based on a multivariate analysis, the presence of moderate or severe LVSD in two-dimensional echocardiography has been shown to increase the prevalence of an acute embolic event, including stroke [14, 15]. Contractile disorders have also been associated with the risk of stroke recurrence [16]. Park et al. [17] reported LVD in more than half of stroke patients, including profound dysfunction in every tenth stroke patient. In such cases, LVD may impede functional recovery of stroke survivors due to their lower exercise capacity.

An adverse implication of limited rehabilitation, regardless of other comorbid diseases, may be the worse post-stroke functional state of stroke survivors. The results of this study indicate that the neurological status on the 1st day after stroke in patients with LVSD was significantly worse than in patients with normal LV function. The consequence of haemodynamic insufficiency associated with LVSD is cerebral hypoperfusion. This impedes the already impaired blood flow in the penumbra area surrounding the cerebral infarction lesion. Other coexisting disorders such as impaired cerebral autoregulation, endothelial dysfunction, prothrombotic state, and infection additionally adversely affect the evolution of the cerebral ischaemic lesion [18–20]. Also, the effect of reperfusion in

Table 2. Neurological status on the 1st day and functional status at 30 days after stroke onset according to selected echocardiographic parameters

Parameter, n	NIHSS	p	mRankin	p
Segmental contractility LV				
normal, n = 127	3.74 ± 4.65	0.013	2.29 ± 1.76	0.10090
abnormal, n = 35	5.40 ± 4.60		2.83 ± 1.82	
EF				
< 50, n = 23	5.67 ± 5.19	0.054	3.08 ± 1.67	0.0386
≥ 50, n = 139	3.93 ± 4.69		2.31 ± 1.79	
EDD				
< 56, n = 142	4.22 ± 4.82	0.379	2.40 ± 1.79	0.4508
≥ 56, n = 20	5.27 ± 4.88		2.82 ± 1.83	
LA				
< 40, n = 98	4.20 ± 4.96	0.592	2.30 ± 1.78	0.4152
≥ 40, n = 64	4.31 ± 4.71		2.53 ± 1.85	
MR				
1–2, n = 104	4.22 ± 4.84	0.811	2.29 ± 1.75	0.6380
3, n = 13	7.00 ± 9.64		2.67 ± 2.08	
AS				
1–2, n = 19	5.56 ± 6.26	0.963	2.38 ± 2.00	0.4372
3, n = 9	3.00 ± 1.63		3.50 ± 0.58	
AR				
1–2, n = 63	4.60 ± 5.47	-	2.56 ± 1.80	-
3, n = 0	-		-	
Concentric RWT hypertrophy				
absent, n = 101	4.46 ± 4.92	0.4393	2.32 ± 1.75	0.3183
present, n = 61	4.02 ± 4.68		2.62 ± 1.86	
Eccentric RWT hypertrophy				
absent, n = 108	4.31 ± 5.13	0.3120	2.48 ± 1.79	0.5536
present, n = 54	4.27 ± 4.01		2.31 ± 1.81	

NIHSS — National Institute of Health Stroke Scale, LV — left ventricle, EF — ejection fraction, EDD — end-diastolic dimension, LA — left atrium, MR — mitral regurgitation, AS — aortic stenosis, AR — aortic regurgitation, RWT — relative wall thickness

Table 3. Neurological status on the 1st day and functional status at 30 days after stroke onset depending on the velocity of mitral inflow E / A

	Group 1 E/A ≤ 0.8 n = 79	Group 2 0.8 > E/A < 2 n = 70	Group 3 E/A ≥ 2 n = 13	1 *vs* 2	1 *vs* 3	2 *vs* 3
NHISS**	3.41 ± 3.36 [0–16] median 3	5.43 ± 5.92 [0–22] median 3	1.67 ± 1.53 [0–3] median 2	0.2388	0.3800	0.2874
Rankin**	2.16 ± 1.67 [0–5] median 2	2.74 ± 1.91 [0–6] median 3	2.33 ± 2.08 [0–4] median 3	0.0445	0.9419	0.6416

** U Mann-Whitney Test; NIHSS — National Institute of Health Stroke Scale

the penumbra zone can be reduced in the presence of left ventricular dysfunction.

According to the results of the present study, an adverse effect on the neurological status on the 1st day after stroke was also brought about by impaired LV filling, indicating left ventricular diastolic dysfunction. The effect of LVDD was independent of coexisting LVLD and EF reduction. It has been previously shown that LVDD, independent of the coexistence of AF, increases the incidence of vascular events and deteriorates patients' status at 3 and 12 months after stroke [17]. The

Table 4. Neurological status on the 1st day and functional status at 30 days after stroke, depending on E / A values of contractile dysfunction and EF

	Group B1 n = 22	Group B2 n = 127	p*
Rankin	3.32 ± 1.81	2.28 ± 1.76	0.0104
NIHSS	8.05 ± 5.92	3.68 ± 4.31	0.0004

*U Mann-Whitney Test; NIHSS — National Institute of Health Stroke Scale

above observations concern patients with cryptogenic stroke. They can result from coexisting with LVDD undetected AF. LVDD is a recognised risk factor for AF, and it can be associated with the progression and symptom severity of AF, and it is also an indirect factor for systemic embolism [21, 22]. Together with LVDD, silent AF can also coexist. According to the results of the present study, E/A dysfunctions have a detrimental effect on patients' functional state one month after the onset of stroke. This sheds new light on the importance of diastolic dysfunction for the possibility of neurological state improvement following acute incidence of cerebral ischaemia. Many studies have shown that LVSD with low EF is only a risk factor for stroke, although there have been reports that do not support such a correlation [23–26]. According to the WARCEF trial, only EF < 15% is associated with an increased risk of stroke (HR 2.125, 95% CI, 1.182–3.818, p = 0.012) [27].

As we have demonstrated in this study, coexistence of low ejection fraction has been associated with adverse effect of LVDD on prognosis in the acute and subacute stage of cerebral infarct. Furthermore, the effect of LVDD varies depending on its severity.

In summary, the results of this study indicate that the presence of LVSD and/or LVDD is a worse prognostic factor in patients in the acute stage of stroke. It has been documented that heart dysfunction (HD) has an adverse effect on the functional status of patients in the chronic stage of stroke, and that this effect is independent of the treatment used, including thrombolysis [28–30].

The results obtained in this study also confirm the independent-of-therapy impact of HD. It is difficult to determine what percentage of stroke patients suffer from HD and are at risk of its decompensation, as well as in which patients HD is likely to have a significant impact on the neurological status. Over-activation of the vegetative system during stroke in patients with preexisting heart disorders may lead to exacerbation of cardiac dysfunction. Due to the differing definitions of HD, prevalence data is inconsistent. Elderly patients with other comorbidities are in the higher risk group [29, 31].

The present study highlights the role of echocardiography in the structural and functional assessment of heart function and in finding abnormalities that may have clinical implications in stroke survivors. TTE may be useful in the planning of post-stroke rehabilitation due to the need to modify it in case of left ventricular dysfunction.

Limitations

The lack of an analysis of the impact of the type of stroke (aetiology) or the size of ischaemic focus on the stroke outcome.

Conclusions

Nearly one quarter of patients in the acute phase of stroke have features of systolic and / or diastolic dysfunction of the left ventricle.

Left ventricular dysfunction adversely affects both neurological status in the acute stage of stroke as well as functional status in the short-term follow-up.

Age at first stroke incidence and lower ejection fraction during the acute phase of illness are predictors of poor functional status one month after stroke.

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Absorbable sutures for the achievement of stable osteosynthesis in surgery for craniosynostosis

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Abstract

Aim of the study. The goal of the present study was to analyse the exclusive use of absorbable suture material (Vicryl) in the fixation of transposed bone segments in cranial vault reshaping without modification of the osteotomy design.

Clinical rationale for the study. In the surgical correction of craniosynostosis, bone fixation using osteosynthesis is a key step. Absorbable osteosynthesis is a widespread tool in cranial vault remodelling, but only a limited number of studies have described the use of absorbable sutures in the treatment of patients with craniosynostosis.

Materials and methods. In 72 children with various types of craniosynostosis, up to 24 months of age, osteosynthesis was conducted exclusively with Vicryl sutures. All patients were evaluated for the stability of postoperative results, and foreign body reactions were examined as part of the routine clinical and radiological follow-up ranging from 1 to 36 months.

Results. All examined children exhibited stable postoperative conditions with immediate stability of all remodelled cranial vaults. 2D and 3D radiological examinations demonstrated good bony union in all cases. Significant foreign body reactions were not observed and bone healing was noted at all sites.

Conclusion and clinical implications. The exclusive application of absorbable suture material enables stable and cost-effective osteosynthesis in craniofacial surgery without altering the osteotomy design.

Key words: craniosynostosis, craniofacial surgery, osteosynthesis, absorbable sutures, cranial vault reconstruction

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Introduction

Craniosynostosis, the premature fusion of one or more cranial sutures, occurs in 1:2,000–2,500 live births, causing typical head shapes depending on the affected suture [1]. The management of craniosynostosis is multidisciplinary but the treatment is principally surgical. The surgical treatment of craniosynostosis consists of osteotomy, bone repositioning and fixation of the affected region using osteosynthesis [2]. There are many different techniques available to correct the deformity.

However, there continues to be a debate over the optimal procedure, timing of surgery and use of osteosynthesis material [3]. Stable osteosynthesis is dependent on immobile fixation of the communicating osteotomy edges and plays a crucial role in the successful outcome of the surgical procedure [4].

Historically, various techniques have been used for rigid fixation, each with different characteristics and properties.

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Simple metallic wire ligatures and metallic plates and screws were among the first materials to be implemented in osteosynthesis [5]. These enabled relatively stable as well as cost-effective fixation of the translocated bone segments [6]. The most common problems encountered when using this method include unwieldy handling, temperature-induced pain, risk of intracranial migration into the growing skull as a result of transposition of the osteosynthesis materials, danger of an injury to the overlying scalp, as well as the disadvantage of removing the material in a second surgical procedure. Recent developments in osteosynthesis materials include titanium microplates which enable simple, well defined and stable fixation [7]. Artifacts in radiological examinations and potential transosseous migration appeared as disadvantages from the use of these non-absorbable plates [8]. These problems seemed to be solved at the end of 1990s with the introduction of biodegradable absorbable osteosynthesis plates and screws composed of absorbable polymers [9]. Their use has been well documented over the past 15–20 years in the craniofacial literature. However, hydrolytic foreign body reaction, loss of tensile strength, less stabilisation and more difficult handling have been reported with the implementation of this method [10]. In addition, reports have shown that the use of absorbable plates increases the operation time due to the extra need for tapping the screw hole and the risk of screw fracture, when the screws are not applied accurately in an orthograde direction [11]. Similarly, published complications associated with resorbable materials are soft-tissue swelling, osteolysis and sterile fistulas, as well as the problem of palpability of the implanted plate resulting in a significant bulge preceding the complete degradation [12]. Studies have shown that the thickness of the plates increases by up to 300% during the degradation process [13].

A promising approach in the field of biodegradable osteosynthesis materials has been employed in our unit for up to 10 years. This simple, stable and cost-effective osteosynthesis method is offered through the correct fixation of displaced bone segments with absorbable sutures. In our department, absorbable sutures are used in the majority of cases to fixate transposed bone segments. Specifically, Vicryl sutures (Ethicon, Slovakia) are implemented in the treatment of craniosynostosis in children up to 2 years of age. Treatment of children over 2 years of age is carried out with polydioxanone sutures (PDS, Ethicon, Slovakia) in order to exploit the extended time of resorption or with resorbable screws and plates.

Clinical rationale for the study

The current study was performed in children up to 2 years of age undergoing cranial vault reconstruction where the fixation of bone segments was performed exclusively with absorbable Vicryl sutures. The surgical procedure remained consistent with that of resorbable plate osteosynthesis. The purpose of the present paper was to accurately investigate and evaluate the overall efficacy of absorbable sutures in our series of craniosynostosis patients.

Materials and Methods

The current study was based on a retrospective design using a standard measurement protocol, examined and approved by the institutional Ethical Committee. The study was carried out according to the Declaration of Helsinki and written informed consent was obtained from the parents. A total of 72 children (39 male, 33 female) with premature closure of at least one cranial suture who were treated with primary cranial vault reconstruction were included in our series. The operations were performed between January 2008 and December 2017.

All cases were carried out by a single craniofacial-paediatric neurosurgical team, and rotating anaesthesiologists and paediatric intensive care specialists assigned to the team. Patient medical records were used to assess the length of surgery, estimated blood loss, average length of hospital stay, and interdisciplinary postoperative follow-up.

58 children with nonsyndromic single suture synostosis were investigated. Moreover, eight children presented with nonsyndromic complex craniosynostosis, and six with a premature suture closure associated with a syndrome (two children diagnosed with Apert syndrome, three with Crouzon syndrome, and one with Pfeiffer syndrome) (Tab. 1).

The average age at the time of surgery was 7.8 months, with a range between 3.5 and 21 months, depending on the involved suture or the patient's individual situation. Postoperatively, patients remained in the paediatric intensive care unit and were transferred to the paediatric neurosurgery ward thereafter.

Table 1. Distribution of involved sutures with summary of patients' demographic data

	Sagittal Synostosis	Metopic Synostosis	Unicornal Synostosis	Bicoronal Synostosis	Multisutural Synostosis	Syndromic Synostosis
Children	36	16	2	4	8	6
Mean age at surgery time	7.4	9.8	8	8.5	7.8	5.1
Mean postoperative hospital stay [days]	5.7	7.8	4.5	6.8	5.3	8.2
Mean follow-up time [months]	24.4	29.4	22	21.3	29.4	30.4
Complications	0	1	0	1	1	0

The average hospital stay was 6.4 days after surgery. The surgical procedure of choice was single stage open transcranial vault remodelling with barrel-staving osteotomies and orbital bandeau advancement as required for existing fronto-orbital dysmorphology. Absorbable sutures were applied to achieve a stable fixation of the transpositioned bone segments through the implementation of absorbable Vicryl sutures, sizes 2–0, 3–0 and 4–0 (Ethicon, Slovakia).

The brain remembers its normal shape. After osteotomy, after the fixation of the bone stenosis was abolished, the brain returned to its normal position. The aim of the stitches was to keep the bones in their new position and to create a normal cranial vault curve during healing. The sutures were applied through the burr-holes. The number of stitches used was as low as possible, usually two on each piece of bone to keep them in their normal position and to fix them with their neighbours.

Follow-up examinations occurred as part of the existing clinical routine protocol. Clinical evaluation was performed by the authors in consultation with a paediatric neurosurgeon and attending neuropaediatrician. Consistency of intraoperatively achieved stability was assessed through subjective inspection and palpation. Additionally, children were examined for possible signs of foreign body reaction specifically manifested through local redness, rejection or systemic reaction. In the postoperative period, routine 2D skull X-rays on a regular basis and 3D CT one year after surgery were conducted, beside standardised anthropometric measurements.

Results

Of the 72 patients meeting the selection criteria of this study, 58 presented with single suture synostosis, and 14 with multiple suture involvement. From those with monosutural synostosis, 36 were discovered to have premature closure of the sagittal suture. Surgical treatment was carried out in one operative setting through open cranial vault reconstruction with or without superior orbital rim reshaping depending on the part of the sagittal suture fusion (i.e. anterior half, posterior half, or both) at the mean age of 7.4 months (Fig. 1). 16 children demonstrated a premature closure of the metopic suture. Surgical approach of choice involved metopic suture release, simultaneous rim advancements, and lateral widening via frontal bone advancement at a mean age of 9.8 months. The two children enrolled in the study with premature unilateral coronal synostosis had a median age of 8 months at the time of operation, and the surgical therapy included simultaneous frontal bone and bilateral orbital rim advancement. Four children with premature bilateral coronal suture synostosis were involved in the study. Fronto-orbital advancement was performed to treat this group as well, at a mean age of 8.5 months at the time of operation.

Eight children with multiple suture synostosis presented to our clinic. The surgical correction of this group of patients was achieved with combined approaches of open cranial vault reshaping (Fig. 2). The average age at surgery was 7.8 months. In addition to the previously described non-syndromic cases, six children with syndromic craniosynostosis who fulfilled the inclusion criteria were included in this analysis. Surgical treatment consisted of complete open skull remodelling with bone transposition, and the average age at surgery was 5.1 months.

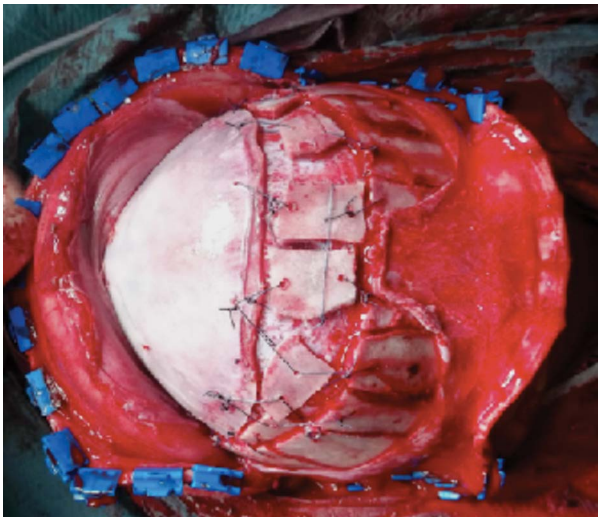

Figure 1. Intraoperatively, supine patient position after stable fixation of bone segments using Vicryl sutures in a child with sagittal suture synostosis and a normal supraorbital region. Superior view

The mean length of postoperative hospitalisation stay of patients with sagittal suture craniosynostosis was 5.7 days. Children with metopic suture involvement were discharged from the clinic an average of 7.8 days after surgery. One patient underwent a prolonged hospital course secondary to wound infection, which was treated with oral cephalexin, and was released after four days. The children in the unicoronal synostosis subgroup left the clinic at an average 4.5 days following surgery. All children after bicoronal synostosis correction left hospital at an average of 6.8 days postoperatively, except for one case who developed a subgaleal hygroma requiring puncture. Discharge of the children with multiple suture craniosynostosis from our department took place 5.3 days after reconstruction. Intraoperatively, one patient from this subgroup, with fusion of the metopic and sagittal sutures displayed sagittal sinus bleed immediately after performing the osteotomies for the orbital bandeau and creation of frontal and parietal craniotomies. Hypotension and brief asystole followed. The child was stabilised through successful local haemostatic techniques and adequate volume resuscitation control of haemorrhage. The patient tolerated the operation well and was observed for an additional seven days for any signs of intracranial bleeding or CSF leakage. Finally, the length of hospitalisation following primary surgery in the group of patients with syndromic craniosynostosis was an average of 8.2 days. No surgically related complications were encountered.

Figure 2. Intraoperatively, final reshaping of bone flaps performed with Vicryl sutures of a 9 month-old child with metopic and anterior half of sagittal suture fusion. The metopic suture fusion did not affect the orbital rims. Lateral view

Wound healing was uneventful during the inpatient period. During the following outpatient clinical course, irritation-free healing of the operative wound was monitored in all patients and all remodelled cranial vaults were stable on clinical palpation. Clinical signs of inflammation or infection in the area of previous surgery were not seen in the complete follow-up period. No signs of foreign body reaction to the resorbable material were observed. Clinical follow-up was carried out for an average of 26.2 months, ranging from 1 to 36 months.

In addition, postoperative cranial imaging including radiographic examination with skull X-ray and CT was performed for an average of 12 months. The follow-up radiographic imaging allowed the evaluation of the degree of ossification as well as the stability of the intraoperative bone relocation. Relevant complications concerning osteosynthesis of the transposed bone segments were not observed, and further interventions were not necessary. The radiographs demonstrated stable postoperative results with a firm bony union and a maintained degree of displacement in all cases. Postoperative dislocations resulting from a loosening or tear of the applied suture material were not observed.

Perioperative and postoperative outcomes were satisfactory in all patients. Parents reported no behavioural or psychomotor abnormalities after surgery. The results on functional, morphologic and aesthetic levels were good. In all cases, the cosmetic outcome was acceptable to the parents during the last follow-up appointment.

Discussion

In the surgical treatment of craniosynostosis, the achievement of stable fixation of transposed bone segments is the foundation of successful therapy. Close, firm and stable communication of the osteotomy edges will lead to direct healing of the bone [15]. Previously published studies based on the use of non-absorbable osteosynthesis material showed unacceptably high rates of complications and morbidity including displacement of the material into the child's growing skull, as well as the need for a second operation for removal of this material.

Over time, the method of osteosynthesis has evolved to witness the replacement of non-absorbable materials such as wire ligatures and titanium microplates with absorbable screws and plates. Most of them are based on resorbable miniplates and miniscrews. The majority of the systems available are derived from polymers and copolymers of glycolic acid, lactic acid and mixtures of D- and L-lactides. Although these resorbable osteosynthesis systems have advanced the technique of bony fixation in craniofacial surgery, some disadvantages have been described.

Published complications associated with resorbable materials include foreign body reactions, soft tissue swelling, reduced stability if the bone exhibits insufficient bone thickness, osteolysis and sterile fistulas [16]. In addition, fractures of absorbable plates have also been reported. Furthermore, during follow-up the number of palpable or visible plates, respectively, increases during the first months up to a maximum of 12 months [17]. It has been reported that the thickness of the plates increases by up to 300% during the degradation process. This initial swelling effect of the resorbable plates which results in a significant bulge preceding the complete degradation has been described by various authors [18].

Basic factors that an osteosynthesis material should fulfill include stability, high biocompatibility, fast and simple use as well as cost effectiveness. Furthermore, the current surgical technique itself should only be marginally changed through the implementation of osteosynthesis material. In addition, the young age of many treated craniosynostosis patients and the unique pattern of cranial vault growth influence the material selection [19].

In the current study, 72 children underwent open cranial vault remodelling with fixation of transposed bone segments performed exclusively with Vicryl sutures (Ethicon, Slovakia). In almost all cases, Vicryl 3–0 and 4–0 was used except for events of an increased tensile load, where Vicryl 2–0 was employed. Long-term follow-up examinations with clinical assessments showed stable osteosynthesis results in all cases. Moreover, foreign body reaction manifesting as local redness, inflammatory skin reaction, rejection or systemic response was not observed in our study group.

The absence of these findings confirms the results of a recent clinical study of 129 patients described by Linz et al. where stable osteosynthesis was achieved absolutely with the use of Vicryl (Ethicon, Germany) suture material. This is in contrast to numerous studies in the literature which describe similar adverse reactions from the use of absorbable plates and screws [20]. According to another clinical study performed by Sanger et al., the complication rates from the use of Vicryl sutures for osteosynthesis were under 1% [21]. This concept was further supported by Gonzalez et al. as they reported a consistent positive assessment with an absence of complications in a group of 37 patients. In our series, follow-up radiographic investigations were employed with 3DCT one year postoperatively and 2D skull X-rays at regular intervals during the first 36 months, and then if indicated until the end of skull growth at the age of 12 years. The outcome in all cases supported the findings of stable bony union without dislocation of the transpositioned segments.

The Vicryl suture material fills the need for a smoother synthetic absorbable suture to facilitate ease of handling, smooth tie down and unsurpassed knot security. Knots are tied with precision and each must hold with proper tension. Adequate strength of the suture material will prevent suture breakage. Secure knots prevent knot slippage and reliable stability is achieved by implementation of stable sutures. According to the manufacturer, at two weeks post-implantation, approximately 75% of the original tensile strength of Vicryl suture remains. The breaking force begins to lessen over a period of 4–5 weeks. Absorption of Vicryl suture is essentially complete between 56 and 70 days.

It should be noted at this point that the use of Vicryl sutures is shown to reduce the cost in comparison to the high material cost for osteosynthesis with absorbable plates. This is in line with today's healthcare environment that requires hospitals to continue to maintain quality standards while lowering material costs to remain financially viable.

Clinical implications/Future directions *Adequate positioning and fixation of the bone segments is a fundamental element in paediatric craniofacial surgery. The data collected and presented in this study has enabled the confirmation of a stable osteosynthesis, with the exclusive use of Vicryl sutures in the reconstruction of children with craniosynostosis up to two years of age. All patients showed a favourable outcome. From a long-term point of view, this series found that Vicryl sutures provide an effective, rigid, well-tolerated and economical alternative osteosynthesis method with satisfying results.*

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Transthoracic echocardiography in the assessment of cardiogenic causes of ischaemic stroke

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Abstract

Introduction. One of the leading causes of death in Poland is stroke. Cardiogenic stroke is known to be one of the most important reasons for acute ischaemic stroke (AIS), comprising 25–30% of all AISs.

Aim of study. Assessment of the prevalence of different risk factors of cardiogenic causes of AIS using transthoracic echocardiography (TTE)

Material and methods. Transthoracic echocardiograms performed in patients with AIS admitted to a single neurological ward between October 2013 and September 2017 were analysed. Patients were assigned, based on the results of their TTE and their previous medical history of atrial fibrillation (AF), to one of three groups depending on the level of the risk of occurrence of cardiogenic causes of AIS.

Ethical permission. According to Dz.U.2001, no. 126, 1381 no ethical permission was needed.

Results. 663 patients with AIS were included in the study. Patients with high risk of cardiogenic cause of AIS: 26.7% (N = 177 patients [p]). Of these, 64.4% (114 p) were diagnosed with AF. 31.6% (56 p) with sinus rhythm during hospitalisation had a history of paroxysmal AF (PAF). In 11.9% (21 p) of the patients qualified to the high risk group, factors other than AF were found. Patients with moderate risk of cardiogenic cause of AIS: 10.1% (67 p). Patients with low risk of cardiogenic cause of AIS: 25.9% (172 p). Echocardiographic results led to a change in therapy in 1.21% of cases.

Conclusions. 1. Transthoracic echocardiography performed routinely in all AIS patients affects the treatment in a very low percentage of cases. 2. The group that could benefit the most from TTE examination includes people without established indications for chronic anticoagulant therapy, in particular patients after myocardial infarction and people with additional clinical symptoms. 3. In patients with AIS, the diagnostic sensitivity of TTE in the detection of PFO is low. Young people with a cryptogenic ischaemic stroke should undergo a transoesophageal assessment.

Key words: stroke, atrial fibrillation, transthoracic echocardiography, cardiogenic stroke, echocardiography
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Introduction

Strokes are one of the leading causes of death worldwide [1]. It is estimated that ischaemic strokes (AIS) account for 87% of all strokes [2]. One of the most common causes of strokes is cardiogenic stroke (25–30% of all AIS) [3]. By definition, a cardiogenic stroke is caused by embolic material entering the cerebral circulation from the heart cavities. This material

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may be thrombi formed as a result of blood flow through the heart, or foreign bodies present in the heart, as well as fragments of tumours or bacterial vegetation. Pathologies that are most often associated with the formation of embolic material in the heart include atrial fibrillation and other conditions associated with the release of blood flow disturbing Virchow's triad with an increased risk of thrombus formation such as aneurysms and post-infarction scars, degenerative valve changes, in particular in the course of rheumatic heart disease, and a non-compacted myocardium.

The risk of a cardiogenic stroke can be divided into several groups, depending on the cause. [3, 4]. The basic examination by which patients can be qualified for a particular risk group is transthoracic echocardiography (TTE). This is recommended for every patient with a suspected cardiogenic stroke [5]. Potentially the greatest benefit of TTE can be experienced by patients in whom the detection of the source of a cardiogenic stroke during the examination would involve a change in the treatment procedure. This group includes patients with thrombi in the left heart cavities and patients with previously undiagnosed atrial fibrillation, in whom the introduction of an anticoagulant therapy significantly reduces the risk of a subsequent stroke [6]. Due to the high mortality rate, which is 10-17% within 14 days [7], and a high relapse rate, it is important to detect the cause of a cardiogenic stroke early and to implement the correct treatment.

Clinical rationale for the study

Assessment of the occurrence of cardiogenic risk factors for the source of acute ischaemic stroke using transthoracic echocardiography.

Assessment of the effect of transthoracic echocardiographic results on treatment change.

Materials and methods

This retrospective analysis included the results of echocardiographic examinations carried out in consecutive patients hospitalised at the Neurological Ward and Stroke Ward with suspected AIS between October 2013 and September 2017. Echocardiography was performed in all patients with initially suspected AIS. A total of 717 studies were analysed. The tests were carried out using Philips Ultrasound Inc. HD11 XE (USA). Echocardiographic measurements and ranges of norms were applied in accordance with generally accepted standards [4]. The physician who performed the echocardiographic examination subjectively assessed study conditions to be 'normal', 'difficult' or 'very difficult' according to the available acoustic window and patient cooperation leading to adequate visualisation of all cardiac structures. Technical difficulties during the examination resulted mainly from anatomical conditions, lack of cooperation, and difficulties in understanding the process in some patients, plus related problems such as the patient's optimal position for the examination. Due to patients' immobilisation and the related difficulty in assessing biometric parameters (height and weight) that would allow the physician to calculate body surface, non-indexed left--ventricular mass (LVM) was used to assess left ventricular hypertrophy (standard: up to 150 g for women, up to 200 g for men), and for the size of the left atrium - the surface area in a four-chamber projection (standard: 18.9 cm^2 for women; 20.3 cm^2 for men) [8]. A concentric hypertrophy was considered when the LVM was above normal at the relative thickness of the left ventricle (RWT) > 0.42. The possibility of diagnosing hypertrophic cardiomyopathy was determined in accordance with current recommendations in patients with a thickness of the interventricular septum > 1.5 cm [9]. Dilated cardiomyopathy was defined as a significant enlargement of the left ventricular end-diastolic diameter (LVEDd) of > 6.0 cm coexisting with left ventricular ejection fraction (EF) < 40% [10]. All echocardiographic examinations were made by one experienced echocardiographer.

The occurrence of AF was assessed based on medical history, ECG examination descriptions, and Holter's ECG tests performed during the hospitalisation.

Based on TTE results and data obtained from medical records, patients were assigned to one of three risk groups of the cardiogenic stroke source:

- High risk group – HR
- Moderate risk group – MR
- Low risk group – LR

The qualification criteria were developed based on literature data. Neurologic and cardiologic (echocardiographic) recommendations are inconsistent [11, 12]. Some divide the risk of cardiogenic sources of embolic stroke into two groups (high and moderate) [4], while others divide it into three (high, moderate, and low [3]). Due to the lack of consensus on this subject, qualification criteria for the above-mentioned divisions were combined and are presented in Table 1 [11, 13–16] Statistica version 13 (Statsoft) was used for statistical analysis. The results are presented as mean (±) standard deviations, and the frequency of occurrence of qualitative variables is given as a percentage. The analysis of variance (ANOVA) using post hoc Shaffe and NIR tests was used to assess the significance of differences between the three analysed subgroups of patients with current risk factors for cardiogenic stroke. The level of statistical significance was considered $P < 0.05$.

Results

The initial analysis included 717 descriptions of TTE research. 54 research descriptions were excluded from the research for the following reasons:

- after the analysis of discharge cards, due to the lack of a definitive diagnosis of ischaemic stroke (49 people),
- due to the patient's death before a definitive diagnosis of ischaemic stroke (three people),

Table 1. Risk of cardiogenic embolism depending on underlying cause

HIGH (HR)	MODERATE (MR)	LOW (LR)
atrial fibrillation	spontaneous echo contrast in heart chambers	patent foramen ovale
mechanical artificial heart valves	severe or moderate degenerative changes in left heart valves	atrial septal aneurysm
rheumatic heart disease	biological artificial heart valve	prolapse of the mitral valve
thrombus in the heart chambers	post-infarction left ventricular aneurysm	features of post-infarction scar (without aneurysm)
infective endocarditis	dilated cardiomyopathy	left ventricular hypokinesia
non-compaction of the myocardium	mitral annular calcification (MAC)	hypertrophic cardiomyopathy
myxoma		

Table 2. Echocardiographic parameters

	Low risk of cardiogenic stroke	Medium risk of cardiogenic stroke	High risk of cardiogenic stroke	P (ANOVA)
Age (years) ± SD	70.5 (± 13)	78.6 (± 10)	77.9 (± 11)	< 0.001 ¥*
Women (%)	37.8	50.7	57.1	< 0.001 ¥
IVSd (cm) ± SD	1.36 (±0.3)	1.34 (±0.2)	1.30 (±0.2)	NS
LVED (cm) ± SD	4.83 (±0.7)	4.80 (± 0.8)	4.81 (± 0.8)	NS
LV mass (g) ± SD	258 (± 89)	252 (± 102)	244 (± 88)	NS
RWT ± SD	0.53 (± 0.1)	0.53 (± 0.1)	0.52 (± 0.1)	NS
EF (%) ± SD	56.3 (± 8.3)	53.1 (± 12)	54.4 (± 9.9)	P = 0.02*
LAd (cm) ± SD	4.16 (± 0.6)	4.21 (± 0.6)	4.56 (± 0.7)	P < 0.001¥#
LAA (cm^2) ± SD	25.6 (± 5.6)	26.9 (± 8.1)	31.8 (± 7.8)	P < 0.001¥#
LAA enlargement (%)	33.7	48.8	97.3	< 0.001¥
LV enlargement (%)	12.2	16.4	14.1	NS
HCM (%)	33.7	26.9	18.6	0.001¥
EF < 35% (%)	2.3	11.9	6.2	NS

Legend: ¥P < 0.05 LR vs HR; #P < 0.05 MR vs HR; *P < 0.05 LR vs MR; IVSd – Interventricular septum thickness at end-diastole; LVED – Left ventricular end-diastolic diameter; LV mass – Left ventricle mass; RWT – Relative wall thickness; LAd – Antero-posterior diameter of left atrium; LAA – Left atrial area HCM – Hypertrophic cardiomyopathy; EF – Ejection fraction

– due to a non-diagnostic acoustic window for echocardiography (two people).

Finally, the analysis included results of examinations of 663 patients with AIS, including 47.8% (317) of women and 52.2% (346) of men. The mean age of patients was 71 years (age range 20–97 years). A summary of the echocardiographic parameters is set out in Table 2.

35.3% (234 patients) of examinations were carried out at the bedside, 26.2% (174) under difficult conditions, and 2.87% (19) in very difficult conditions. The most common abnormalities found in echocardiography were left ventricular hypertrophy and left atrial enlargement.

In the studied group, 65.2% of the patients (432 patients) had concentric left ventricular hypertrophy. In 20.1% of the patients (133), the concentric hypertrophy reached values that met the criteria for diagnosing hypertrophic cardiomyopathy based on the IVSd measurement in accordance with the recommendations of the European Society of Cardiology [17]. In 10.7% of the patients (71), eccentric hypertrophy of the left ventricle was found in the examination.

The incidence of enlargement of the left atrium depends on the used assessment method. The antero-posterior diameter (LAd) exceeded norms in 70.3% of the patients. Using the planimetric method (LAA - left atrial area), left atrial enlargement was found in 85.2% of the patients. Among this group of patients, 117 people (25.1%) were diagnosed with atrial fibrillation.

HR group

The patients with a high risk of a cardiogenic stroke source constituted 26.7% of all the subjects (177 people).

The mean age in the high-risk group was 77.9 years. 57.1% of the patients (101 people) in this group were women. The main factor qualifying for the HR group was the occurrence of atrial fibrillation (96%, 170 people). In 64.4% of the patients (114 people) from the HR group, atrial fibrillation occurred during echocardiography. 31.6% of the patients (56 people) with a sinus rhythm during echocardiography were qualified for the HR group due to paroxysmal atrial fibrillation diagnosed earlier or during hospitalisation.

In 11.9% of the patients (21 people) qualified for the HR group, non-AF factors of a high risk of a cardiogenic stroke source were detected, and in this group seven patients (four with an intracardiac thrombus, two with a mechanical valve, and one with a rheumatic defect) suffered from the co-occurrence of atrial fibrillation.

Finally, in 14 people (2.1% of the entire group), factors of a high risk of a cardiogenic stroke source other than atrial fibrillation were found: thrombus in left heart cavities (six people), presence of left-sided mechanical valve (five people), and one person with infective endocarditis (IE), left ventricle non-compaction, and a rheumatic heart defect.

MR group

The patients with a moderate risk of a cardiogenic stroke source constituted 10.1% of all the subjects qualified for the examination (67 people). 50.7% (34 people) of the MR group were women. The mean age in the moderate risk group was 78.6 years.

The most common causes qualifying for the MR group included: occurrence of severe degenerative changes on left-sided valves (52 people, 77.6%), including 34.3% (23 people) with mitral annulus calcification (MAC). Other causes were less frequent: dilated cardiomyopathy (seven people), left ventricular post-infarction aneurysm and a biological valve (two people), spontaneous contrast in heart cavities (one person).

LR group

The patients with a low risk of a cardiogenic stroke (LR group) constituted 25.9% of all the subjects (172 people), of which women accounted for 37.8% (65 people). The mean age in this group was 70.5 years. One of the qualification criteria for this group was diagnosing persistent foramen ovale (PFO), which was detected in three people (0.45% of all the patients).

Other results

In 37.3% of the subjects (247 people) no potential causes of the cardiogenic stroke source were found. The mean age in the studied group was 65.3 years, and women accounted for 47% (116 people).

A group of 10 people (1.5% of those who were included in the study) was identified among the patients, whose TTE image indicated the presence of a thrombus in the left heart cavities. The mean age in this group was 69.6 years, and nine out of 10 were men. The mean ejection fraction of patients with a thrombus in the heart cavity was 41%. Based on the echocardiographic image, previous myocardial injury was found in eight patients from this group. Moreover, the group was characterised by the presence of many comorbidities such as arterial hypertension (six people), cardiomyopathy (two people), ventricular arrhythmias (two people), renal failure (two), and type 2 diabetes (three people).

Discussion

The research that we have conducted is one of the largest available in the literature on the subject, and the first one describing the Polish population and analysing the role of an echocardiographic assessment in patients hospitalised due to acute ischaemic stroke. The echocardiographic examination that is often recommended and performed in patients with AIS seems to have little effect on further proceedings in this group of patients.

During the study, only in 1.21% of all the patients did the TTE result influence a change in treatment. This percentage can be compared to the result obtained in similar research carried out at the Duke University Medical Centre, where the TTE result, subsequently confirmed by TEE, was associated with a change in treatment in 1.52% of patients (four people) [18]. The change in treatment mainly concerns patients with a thrombus in the heart cavity or myocardial non-compaction, without other indications for an anticoagulation therapy and patients with valvular heart diseases that require surgical treatment, including active IE.

Undoubtedly, the most frequent cause of formation of thromboembolic material in the heart cavities, which may become a cardiogenic stroke source, is atrial fibrillation [11]. AIS is the basic complication of AF that worsens the prognosis and is the cause of increased mortality in this group. Electrocardiographic examinations (resting, Holter) are used to diagnose AF. Due to the fact that all patients diagnosed with atrial fibrillation and AIS (25.6% of the patients in the research) have indications for chronic anticoagulant therapy, in their case the result of the echocardiographic examination will rarely be associated with a change in secondary prevention of AIS [9]. A similar conclusion can be drawn from research that used transoesophageal echocardiography which was conducted at university hospitals in Berlin on patients after an ischaemic stroke, both with documented AF and without such a diagnosis. Only 3.8% of the patients with AF were diagnosed with embolic material during TEE, the origin of which could not be explained by co-occurring atrial fibrillation. However, this did not change the treatment in any of these patients, and the echocardiographic findings had no effect on the prescription of anticoagulants or a change in the anticoagulant therapy used at that time [19].

Considering the above results, performing TTE in patients with an ischaemic stroke and a diagnosed AF should be limited to people with additional disturbing symptoms such as a heart murmur or a fever suggestive of infective endocarditis.

Patients with AIS without any previously diagnosed atrial fibrillation or other indications for an anticoagulant therapy are a separate group. Although TTE is not a tool that allows a diagnosis of atrial fibrillation, it helps to distinguish those patients who are at risk of this arrhythmia. Left atrium enlargement, mitral valve defects, increased left ventricular hypertrophy, or the presence of pulmonary hypertension

found during echocardiography are all recognised risk factors for paroxysmal AF, which can remain subclinical for a long time. The first manifestation of arrhythmia is sometimes an ischaemic stroke [20–27]. Assessing the size of the left atrium seems particularly useful. In our research, enlargement of the left atrium assessed by the surface area (LAA) occurred in 97.3% of the patients in the HR group, whereas enlargement of the left atrium assessed with the use of LAd occurred in 83.5% of the patients in the HR group, in which people with AF predominated. Therefore, planimetric assessment of left atrium size should be preferred. Left atrial volume calculation, which is preferred in the guidelines, requires BSA calculation, which can be challenging in this population [28]. Patients with a significant left atrial enlargement could potentially benefit from prolonged electrocardiographic monitoring that would optimally last longer than seven days which, although recommended in guidelines, is still not available in Polish conditions [11].

Patients who have had a myocardial infarction and do not use an anticoagulation treatment are a special group that could benefit from echocardiographic assessment. In our research, of a group of 10 patients with thrombi visible in the TTE, eight had traits of post-infarction myocardial injury in the echocardiographic examination.

Another group that can also benefit from an echocardiographic examination is young patients with a cryptogenic stroke. In these patients, the detection of a patent persistent foramen ovale (PFO) with a documented right-left leak may be an indication for percutaneous closure to avoid recurrent AIS episodes [6–8, 29]. The transthoracic examination allows a certain diagnosis of PFO only in a minority of cases. Therefore, in patients with suspected persistent foramen ovale, with a normal heart image in TTE, it is indicated to perform transoesophageal echocardiography (TEE) [11]. In the analysed group, only 0.45% of all the subjects during the TTE had persistent foramen ovale. Comparing this to the population occurrence of PFO, which amounts to 20–28%, [30, 31] shows a low diagnostic sensitivity of TTE in detecting PFO, especially in technically difficult bedside tests. Therefore, young people with a real cryptogenic strokewho are potentially eligible for PFO closure treatment should be qualified for a transoesophageal examination, which is usually made after an earlier transthoracic examination.

If a cardiogenic stroke source is suspected, it has been recommended that treatment start as early as possible to allow the diagnosis of a possible thrombus and to implement appropriate treatment as soon as possible [5]. The implementation of recommendations within 24 hours appears challenging. The limited availability of echocardiographic imaging, and the increasing use of echocardiographic laboratories, indicate a need for a careful selection of patients for this examination.

Communication between the neurologist ordering the treatment and the doctor performing the echocardiography is very important. The echocardiography order should contain basic information on the history of the cardiovascular system diseases, in particular: diagnosis of atrial fibrillation, previous myocardial infarction, and other factors that may suggest rare causes of cardiogenic attacks (e.g. fever in IE). Information on the cryptogenic nature of AIS, in particular in young people, may also be important. It is also useful to provide a patient's weight and height, if known, which allows some echocardiographic parameters to be referred to the patient's body surface.

The limitations to our publication include: difficult conditions of echocardiographic assessment resulting from the specifics of a studied group; lack of possibility to measure patients' height and weight due to their severe clinical conditions, and thus the lack of the possibility to scale the size of the heart cavities in relation to the patients' biometric size, including the assessment of the volume index recommended in the guidelines of the left atrial size parameter. Due to the lack of complete data, our publication did not include the nature of ischaemic changes in imaging (CT MRI) and clinical scales of stroke severity.

Conclusions

1. Transthoracic echocardiography performed routinely in all AIS patients affects the treatment in a very low percentage of cases.
2. The group that could benefit the most from TTE examination includes people without established indications for chronic anticoagulant therapy, in particular patients after myocardial infarction and people with additional clinical symptoms.
3. In patients with AIS, the diagnostic sensitivity of TTE in the detection of PFO is low. Young people with a cryptogenic ischaemic stroke should undergo a transoesophageal assessment.

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Brain abscess and pyocephalus: our experience with treatment

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Abstract

Introduction. Pyocephalus always presents serious complications in the treatment of brain abscesses, and is associated with high rates of mortality and morbidity. This study aimed to comprehensively evaluate this understandably feared complication from a purely medical perspective by using an evidence-based approach and drawing comparisons from the available literature, which mostly comprises case reports.

Methods. This was a prospective monocentric study of all patients treated for brain abscesses at the Neurosurgery Clinic of the University Hospital Ostrava between 2012 and 2017. The cohort was divided into two groups for statistical comparison; one group comprised those in which pyocephalus occurred before or during treatment, while the other group comprised patients without this complication. Particular consideration was given to the effect of pyocephalus on morbidity and mortality rates and C-reactive protein levels, as well as to the identification of risk factors, and to its possible therapeutic influence. Patients were followed up for six months.

Results. A total of 43 patients were treated for a brain abscess. An unequivocal diagnosis of pyocephalus was established via CT and MRI brain scans in five cases (11.6%). In the cohort as a whole, mortality and morbidity rates were 23.3% and 48.8% respectively. Among patients with pyocephalus the incidence of mortality and morbidity was 40% and 66.6% respectively. The presence of pyocephalus is not a significant predictor of either morbidity (p 0.575) or mortality (p 0.664). In patients with pyocephalus, we determined elevated CRP levels on the day of surgery (p 0.038). The occurrence of epileptic seizures in the acute phase of the disease is associated with a poor outcome (p 0.039).

Conclusions. Pyocephalus will continue to be a serious complication in the treatment of brain abscesses, although we were unable to determine its utility as a prognostic factor. Patients with this complication have elevated CRP levels on the day of operation.

Key words: brain abscess, pyocephalus, mortality, ventriculitis, intraventricular rupture
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Introduction

A brain abscess is a serious inflammatory illness with an uncertain prognosis. Treatment outcome is influenced not only by a range of underlying factors including age at onset, associated diseases and immune system status, but also by the localisation of the abscess. For example, an abscess close to the ventricle can rupture, leading to the spontaneous effusion of pus into the ventricular system, with the resultant ventriculitis manifesting as sepsis or even septic shock. A diagnosis of pyocephalus can be made initially or as it arises over the course of treatment and is frequently associated with sudden clinical deterioration. The risk of this complication is considered to be higher with the presence of multilocular or deep-seated abscesses close to

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the ventricles [1], and can occur in as many as 35% of cases [1, 2]. Mortality rates are high, ranging from 40–85% [1–4]. In addition to the standard therapies presently carried out, the treatment of pyocephalus can involve ventricular drainage to discharge purulent CSF accompanied by the intraventricular administration of antibiotics, with glycopeptide vancomycin being the one most commonly recommended in case studies [5, 6]. Even so, an established therapeutic strategy for this special subgroup of patients remains controversial, being led as it is by empirical experience of the workplace and each individual patient's clinical development.

Methods

Study design

This prospective monocentric study was carried out at the Neurosurgery Department of the University Hospital Ostrava between 2012 and 2017, and comprised all patients who received treatment for a brain abscess during this period. The diagnosis was confirmed upon admission by imaging studies. Initial CT scans were performed on all patients, supplemented by MRI conducted according to the standard protocol consisting of T1- and T2-weighted images, FLAIR, DWI with application of contrast material as standard and also spectroscopy sequencing. For a positive diagnosis of abscess it is always necessary to observe restriction on diffusion-weighted images while taking into account clinical condition and laboratory findings.. Patients with pyocephalus were assigned to one study group, while a second group comprised patients without this complication. Therapeutic algorithms were identical in both groups: initial broad-spectrum empirical antibiotic treatment was modified according to culture findings, preliminary laboratory findings and the establishment of inflammation markers (CRP) while always investigating the origin of the abscess and carrying out surgical treatment. All patients underwent surgery within 24 hours of diagnosis. The type of operation was chosen according to the localisation and the patient's clinical condition. Guided aspiration was carried out on deep-seated lesions in affected areas and residua surgically excised, with samples of the purulent fluid taken away for culture. We carried out external ventricular drainage (EVD) on patients with pyocephalus (excepting that this procedure was not indicated for one patient who was in good clinical condition). Patients were followed up for six months. Outcome was determined on the basis of the modified Rankin Scale (mRS) (Tab. 1). This study was approved by the local Ethics Committee.

Statistical evaluation of the study group

Statistical comparison was carried out using the IBM SPSS (version 25) statistics program. We focused on morbidity and mortality rates, risk factor identification and potential treatment complications including epilepsy, intraventricular drainage and hydrocephalus.

Table 1. Outcome after six months

mRS	n = 43
0	17
1	2
2	0
3	5
4	7
5	2
6	10

Results

Outcome

A total of 43 patients (24 male, 19 female) were treated, including four children. The average age was 45 years for men and 55 for women. The youngest patient was a 5 year-old boy, the oldest an 86 year-old woman. Pyocephalus was clearly determined by CT and MRI scans in five patients (11.6% of cases). Overall mortality in our study reached 23.3%, while the morbidity rate was 48.8% (mRS 1–5). Among patients with simple abscess, the mortality rate was 21% and morbidity 36.8%. The causes of death were four cases of accented perifocal oedema accompanied by rapid craniocaudal deterioration, one case of extensive bleeding along the puncture trajectory, two cases of progressive sepsis and one case of cardiopulmonary failure. Among patients with pyocephalus, mortality was 40% and morbidity 66.6%. In our study, pyocephalus was not a statistically significant predictor of either morbidity (p 0.575, exact test) or mortality (p 0.664, exact test). Two patients with pyocephalus died within 14 days with symptoms of persistent sepsis and progressive multiple organ failure. One patient successfully underwent CPR following spontaneous ventricular fibrillation on the eighth day of treatment. Regarding the morbidity of cured patients, there were two instances of residual hemiparesis and psycho-organicity (mRS 3), and one case without any long-term ill effects (mRS 0). Patient characteristics, along with surgical procedures and culture findings, can be found in Table 2.

Seizures

Five patients (11.6%) had multiloculated lesions, of which one patient had pyocephalus. The remaining 88.4% had uniloculated lesions. The total number of lesions was 50. Most were located at the frontal lobe (38%, epilepsy risk p 0.309), followed by the temporal lobe (22%, p 0.778), occipital lobe (14%, p 0.904) and parietal lobe (12%, p 0.524). 4/50 were at deep-seated structures such as the basal ganglion and brainstem (8%, p 0.267), with 3/50 at the cerebellum (6%, p 0.224). The effect of abscess location on the incidence of epileptic seizure could not be determined.

Table 2. Characteristics of patients with pyocephalus

Pacient with pyocephalus (age / sex)	Initial symptoms	Origin of infection	Localisation	Treatment	EVD	Culture findings	Predisposing factors	Outcome
44 / M	sopor, neck stiffness	middle ear	right temporal lobe	excision	yes	Prevotella sp., Bacteroides sp.	alcoholism	mRS 6
53 / M	fever	unknown	left basal ganglia	aspiration	yes	Streptococcus intermedius	hypertension	mRS 3
77 / F	somnolence, hemiparesis	unknown	right parietal lobe	excision	yes	Streptococcus intermedius	hypertension	mRS 6
39 / M	coma	dental infection	right thalamus, cerebellum, right P lobe	aspiration 3x	yes	Fusobacterium nucleatum	alcoholism, diabetes	mRS 3
5 / M	neck stiffness, fever	repeated respiratory infection	left frontal lobe	aspiration	no	negative	none	mRS 0

The frequency of epileptic seizures, both generalised and partial, was noted over the six-month monitoring period. 32.5% of patients (14/43) were symptomatic in the acute phase of the illness. Ten patients exhibited partial seizures, with generalised seizures in the remaining four, while 11 cases exhibited one-off incidences in the initial or early stage of the illness up to 72 hours post diagnosis, with no recurrence following treatment. In one case it was necessary to place the patient in a barbiturate-induced coma after suffering status epilepticus. This patient died shortly thereafter from cardiorespiratory complications. The period prescribed for anti-epileptics did not exceed that of antibiotics (a maximum of six weeks). Just one patient required long-term medication for chronic epilepsy after the conclusion of treatment. The occurrence of epileptic seizures in the acute stage of the illness is an indicator of a poor long-term prognosis (p 0.039, $\chi 2$ test), as are persistent mRS values in the range 2–5 with various presentations of hemiparesis, and impaired psychological and language function being most typically described. It was not found to affect mortality rates (p 1.000, exact test).

Surgical approach

Guided aspiration of lesions was carried out in 51.2% (22/43) of cases. There were six reoperations among this subgroup: three punctures were carried out repeatedly on one patient who had pyocephalus; one operation was extended to include excision after adverse MRI findings postoperatively; one revision of puncture trajectory was performed due to haematoma, and in another case it was necessary to perform hemicraniectomy for accentuated perifocal oedema. Excision was primarily performed in 48.8% (21/43) of cases. In three cases, reoperation was performed 14 days after the primary operation following ambiguous findings on postoperative MRI studies (i.e. partial persistence of diffusion restriction and no indication of regression in lesion size). In another case, acute revision was necessary due to haematoma in the surgical field with the onset of herniation.

Table 3. Origin of infection

Origin of infection	n = 43 (100%)
unknown	11 (25.6%)
paranasal sinusitis	6 (14%)
otitis media	4 (9%)
haematogenous	9 (21%)
complication of therapy (iatrogenic)	7 (16.3%)
dental	6 (14%)

Laboratory findings and origin of infection

Average initial CRP levels were 26 mg/l in patients without complications and 82.4 mg/l in those with pyocephalus. Physiological CRP was present in 19 of our study patients (44.1%) on the day of operation (< 8 mg/l). We determined statistically higher CRP levels in patients with pyocephalus (p 0.038, median test).

The underlying cause of the abscess could not be established in a quarter of patients. The most common source was haematogenous spread, followed by infection of the paranasal sinus and teeth. The least common cause was middle ear infection. We noted abscess progression as a postoperative complication in seven patients (Tab. 3). Culture remained sterile in 51.1% of samples. No mycotic or tuberculous abscesses were treated during this study. Two cases of extended cultivation eventually isolated aerobic Nocardia (Tab. 4). In the pyocephalus subgroup, positive culture was found in 80% of cases, with one patient in a good clinical state and culture-negative. This was due to intraventricular rupture occurring some time after antibiotic therapy with the patient's condition not indicating drainage. The remaining patients had initial pyocephalus. In these we carried out aspiration to evacuate pus from the affected lateral ventricle. In two patients this was performed as part of the primary operation prior to abscess

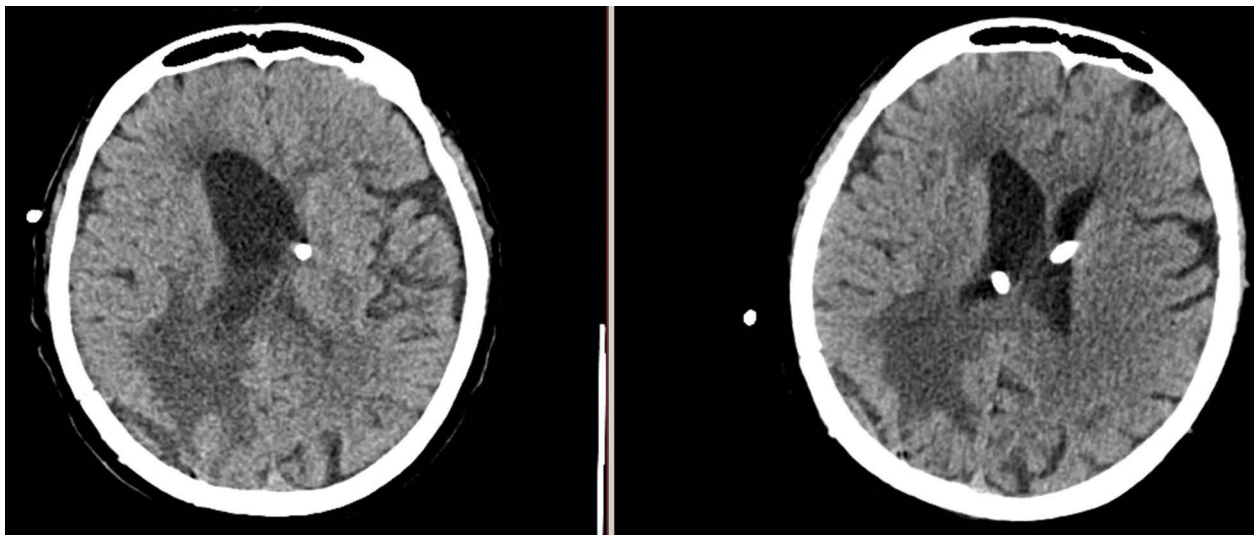

Figure 1. Bilateral external drainage in a patient with isolated lateral ventricles

Table 4. Culture findings

Culture findings	n = 43 (100%)
aerobic origin	7 (16.3%)
anaerobic origin	6 (14%)
mixed cultures	8 (18.6%)
atypical	0
sterile cases	22 (51.1%)

excision. In the remaining two this was performed some time later on the basis of ventricular progression observed by imaging studies. In one case we performed drainage of both ventricles for a bilateral foramen of Monro obstruction (Fig. 1), although this patient died soon after. The remaining patient underwent EVD two days postoperatively for the progression of unilateral hydrocephalus affecting the left lateral ventricle (Fig. 2). In this case, the drain was left in place for four weeks. Repeated attempts to remove were unsuccessful due to the isolated nature of the left lateral ventricle – the situation was resolved by performing guided endoscopic septostomy from the right-hand side. In another surviving patient the drain was left in place for 14 days, after which it was discontinued due to malplacement causing patient discomfort. Regular MRI follow-up found the ventricular system to be stable. VP shunts were not required on any patients in the study. We did not administer antibiotics intraventricularly — all patients were treated intravenously as is standard, initially with the recommended combination antibiotic therapy (2–3 g cefotaxime with 0.5 g metronidazole every eight hours; vancomycin separately in the case of postoperative complications) adjusted as necessary according to culture.

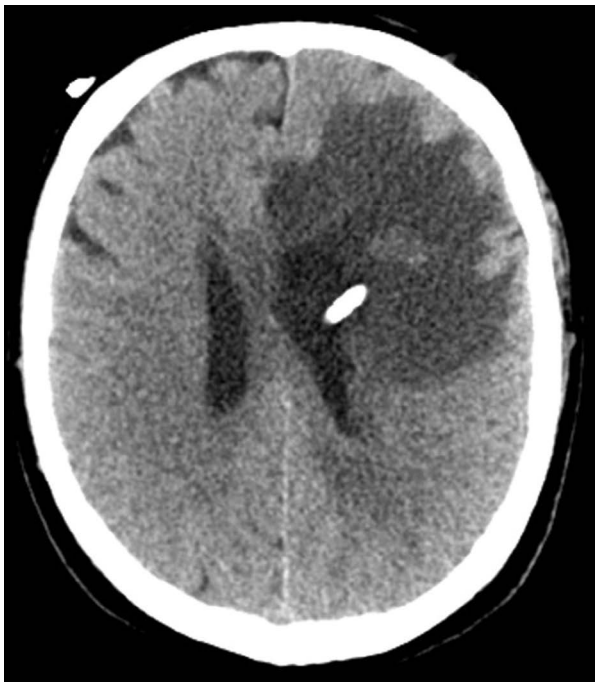

Figure 2. CT image of drained lateral ventricle in a case of unilateral hydrocephalus. Complication was resolved by performing guided endoscopic septostomy

The study included seven immunocompromised patients (16.3%), none of whom had pyocephalus. In one patient this was due to kidney transplantation, and two others were undergoing radio- and chemotherapy. The remaining four patients were chronically immune-suppressed due to rheumatoid arthritis. Immunosuppression did not affect either morbidity (p 0.240, exact test) or mortality (p 1.000, exact test). The most commonly-occurring underlying diseases

were hypertension in 18 patients (36%) and diabetes in six patients (12%). Neither hypertension (p 0.322) nor diabetes (p 0.526) had any effect on mortality rates.

Discussion

Outcome and factors related to outcome

Even with improved imaging techniques and a variety of specific neurosurgical approaches at our disposal, brain abscesses remain a diagnosis with a highly uncertain prognosis that is dependent on their localisation. Overall condition, age and accompanying illnesses all play an important role in treatment outcome.

Our findings concerning mortality and morbidity rates are consistent with current experience. Statistically, the presence of pyocephalus and immuno-suppression did not influence the outcome, nor could we determine that immunosuppression has an influence on the incidence of pyocephalus. The most common underlying conditions were hypertension and diabetes (36% and 12% respectively). We could not determine if these factors affected the outcome. Xiao et al studied 178 patients treated between 1986 and 2002 and described only four patients with pyocephalus, two of whom died during the study. Neither pyocephalus, diabetes nor cirrhosis were found to effect the outcome. Only initial GCS, immunodeficiency and the presence of underlying disease were found to have a significant influence on the outcome [7]. In the discussion of the range of epidemiological factors involved, we can refer to a retrospective study of brain abscess cases from 2002–2017 conducted by Amornpojnimman et al in Thailand.The authors considered immunosuppression to be the most significant risk factor in the formation of abscesses. Confusion as a symptom of septic encephalopathy is associated with a poor outcome (GOS 1). In this study, there was a high proportion of immunocompromised patients (42%), although this figure included patients with diabetes (16%). This study also included 10 cases of HIV (12.3%), as opposed to none in our study. There was only one case of spontaneous pyocephalus (1.2%). The most frequently-occurring complication mentioned was hydrocephalus, in 17.3% of patients, but the study lacked a further appraisal of the treatment or information as to whether EVD was necessary [8]. Kao et al reported that short duration of symptoms, diabetes and cirrhosis were associated with poor outcomes in 53 patients [9]. Another study by the Thai authors concluded that spontaneous intraventricular rupture and fungal abscesses were predictors of a poor outcome [10]. A series of earlier case studies considered pyocephalus as a malign symptom associated with an adverse outcome [2, 3, 6]. In a study of 179 patients treated between 1986 and 2005, Lee et al identified the risk factors predictive of ventricular rupture to be size and multiloculation of abscesses, and their proximity to the ventricular system. This study included a high overall incidence of intraventricular rupture (34.6%). 25.2% of patients were initially diagnosed and 9.4% were diagnosed over the course of treatment. Mortality among this subgroup of patients was 26.7% at three months. The surgical therapy described for this cohort consisted of stereotactic aspiration or excision; this study does not mention if EVD was eventually necessary, or if there were complications in terms of hydrocephalus [1].

Treatment modalities of pyocephalus

Ventricular drainage may be performed on the basis of the patient's clinical state, imaging findings and the response to routine antibiotic therapy. Drainage was not indicated in one patient in good clinical condition in which pyocephalus occurred three weeks after treatment for purulent meningitis, accompanied by severe headaches and fever and the recurrence of meningeal irritation. In the remaining patients, drainage was required for a possible unilateral foramen of Monro obstruction causing hydrocephalus. Black et al described a similar experience in the treatment of a ruptured thalamic abscess, although with complications arising five weeks after the commencement of treatment [11]. Brewer et al recommended drainage as a routine therapy in a paper published in 1975 [12]. The intraventricular administration of vancomycin has been presented as a successful treatment for pyocephalus in a number of previous case studies [6, 13, 14] although this approach has been unsuccessful in other cases involving gentamicin [15]. Two patients died early on in our study from ongoing sepsis and multiple organ failure. The cause of death was not hydrocephalus and even prompt and aggressive antibiotic therapy was ineffective.

While we believe this approach remains the most appropriate in such cases, it does mean that improving patient outcome will, for the time being, continue to be problematic. The appropriate surgical technique depends on the localisation and the character of the findings. All of these patients were culture-positive, therefore we can assume active inflammation and the possible inefficacy of antibiotic therapy. Furthermore, the permeation of antibiotics into a developed, encapsulated abscess remains debatable and the therapeutic effect impossible to determine directly. Only cefotaxime, ceftazidime, imipenen and metronidazole have been proven to penetrate the abscess capsule *in vivo* [16–19]. A rare minimally-invasive approach is presented by Nishizaki et al, where the patient successfully underwent evacuation of the intraventricular abscess using a neuro-endoscope. The material was collected for bacterial culture, resulting in gentamicin sulphate being administered twice daily for nine days in combination with intravenous cefotaxime sodium for 14 days. The patient made a full recovery [20].

Vancomycin is the subject of most research in the intraventricular administration of antibiotics. It is considered to be safe in a wide range of doses, from 0.075–50 mg per day. 5–20 mg is the most frequently recommended daily dose to

achieve a sterile fluid. Only a few instances of side effects have been noted, such as leukocytosis [21] and severe headaches when administered via an Ommaya reservoir [22]. The pharmacokinetics of vancomycin in the ventricular system are unclear, relying as they do on several possible population models, with a range of complicating factors including severe infection, obstruction of CSF flow in hydrocephalus or the presence of drainage [5].

Laboratory findings

Elevation of inflammation markers in abscesses tends to be unspecific and does not reflect the severity of the illness. Infections in isolated compartments such as the CNS as protected by the blood-brain barrier induce only minimal or slight system changes that can be detected in serum, as reflected in our findings — physiological CRP levels were found in 44.1% of our study patients. Helweg-Lareson et al conducted a retrospective study of 102 patients and found that 26% of the cohort had low CRP (< 20 mg/l) and that 49% were without leukocytosis. CRP levels were not found to influence outcome [23]. Similarly, Ko et al, in a retrospective study, found initial CRP values to be normal in 39% of the study group [24]. We determined statistically higher CRP among patients with pyocephalus on the day of surgery. However, the current lack of similar published studies means it is not possible to corroborate these findings.

Severe ventriculitis resulting in sepsis, being the system's reaction to insult, elevates acute inflammatory parameters in serum, as consistent with our findings. CRP cannot therefore be taken to be a reliable indicator of a successfully treated infection, and should only be used to supplement imaging and clinical findings in the decision to end antibiotic therapy.

Localisation

Regarding the supratentorial and infratentorial regions, brain abscesses occur overwhelmingly more frequently in the former. We found abscesses to be most commonly localised in the frontal or frontoparietal lobe, as consistent with other studies [1, 7, 25]. In a cohort of 51 patients, Cavusoglu et al demonstrated its typical occurrence in the temporoparietal lobe [26].

Seizures

Epileptic seizures in the acute phase are relatively common, occurring in 13-50% of patients [1, 7, 9, 27–30]. 30–50% of patients are at risk of late seizures or chronic epilepsy [27–31]. In a three-year study, Buonaguro et al described late seizures in 7/29 children (24%) [32]. In our study, there was just one patient who experienced repeated seizures requiring combination antiepileptics after six months. The remaining initially symptomatic patients were prescribed anticonvulsants until the conclusion of antibiotic therapy and for a maximum of three months. Abscess localisation in the frontoparietal lobe is a possible risk factor [33], although this could not be confirmed in our study.

It is also necessary to consider the role of medication in inducing seizures: Martin-Canal et al documented a significantly higher incidence of convulsions in patients treated with imipenem compared to meropenem, and recommended this and carbapenem in such cases. The pharmacokinetic and microbial effect is thought to be broadly similar if not identical. Additionally, no seizures were noted in a group administered only metronidazole and cephalosporins [34]. In children, the administration of anticonvulsants should be individualised on the basis of EEG monitoring [30]. Most authors recommend the prophylactic prescription of medication for three months [35]. One possible weakness of the study is the six-month follow up period, given the potential for the late onset or recurrence of seizures, especially in children. At least two years of follow up is required to properly evaluate this complication.

Conclusion

Although its prognostic value remains uncertain, we do know that pyocephalus will continue to be a serious complication in the treatment of brain abscesses, initially requiring prompt and aggressive antibiotic therapy supplemented by surgical treatment of lesions. We find EVD to be an appropriate procedure for the aspiration of purulent material, and useful for both the prevention of acute hydrocephalus and the possibility of directly administering antibiotics. We were unable to identify any risk factors associated with the development of this complication. These patients have statistically higher CRP on the day of operation. The occurrence of epileptic seizures in the acute phase of brain abscess treatment is a poor prognostic factor.

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Successful subthalamic stimulation after failed gamma-knife thalamotomy in the treatment of tremor-dominant Parkinson's disease

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Here, we present the case of a 63 year-old right-handed man with an 11-year history of a tremor-dominant Parkinson's disease (PD) with severe rest and postural tremor in the right extremities, especially in the right hand. The initial response to pharmacological treatment was good. Levodopa test performed one year after diagnosis was positive. The motor part of Movement Disorders Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS) was 12 scores in medication off condition and 5 scores in medication on condition [1]. The patient's daily levodopa dose was 400 mg. He took rasagiline 4 mg daily and trihexyphenidyl 2 mg per day. Trihexyphenidyl was soon stopped due to severe dizziness. This daily levodopa dose also caused dizziness, lightheadedness, and weakness symptoms indicating low blood pressure. His blood pressure ranged between 90/60 or even below. Moreover, he also experienced falls due to orthostatic hypotension. These side effects constituted the main reason to discontinue levodopa intake. He had significant cardiac comorbidity with congestive cardiomyopathy and end-stage heart failure functional class IV according to the New York Heart Association (NYHA) functional classification. At the age of 56 he underwent successful orthotropic heart transplantation.

Over the following years, his untreated PD symptoms progressed on both sides of the body, especially the right-sided tremor and the right-sided rigidity, making eating, drinking, and washing as well as shaving impossible. Efforts to introduce levodopa or dopamine agonists again were unsuccessful, due to a burning pain in the chest occurring immediately after the medication consumption. The patient scored 33 points in medication off condition on the MDS-UPDRS part III. In an effort to reduce tremor and improve quality of life, a left Vim GKT (Gamma-Knife Thalamotomy) was performed using a Leksell Gamma Knife Perfexion system after obtaining informed consent (Figure 1A). Over the following 12 months the right-sided tremor persisted and handicapped him in the performance of daily living. 18 months after the radiosurgical treatment he was scored 28 points on the MDS-UPDRS part III. Magnetic resonance imaging showed typical good demarcated lesion with ring contract enhancement (Figure 1B). Because of persistent and severe right-sided tremor, the patient opted for a Deep Brain Stimulation (DBS) procedure. The left subthalamic nucleus (STN) was selected as the stereotactic target.

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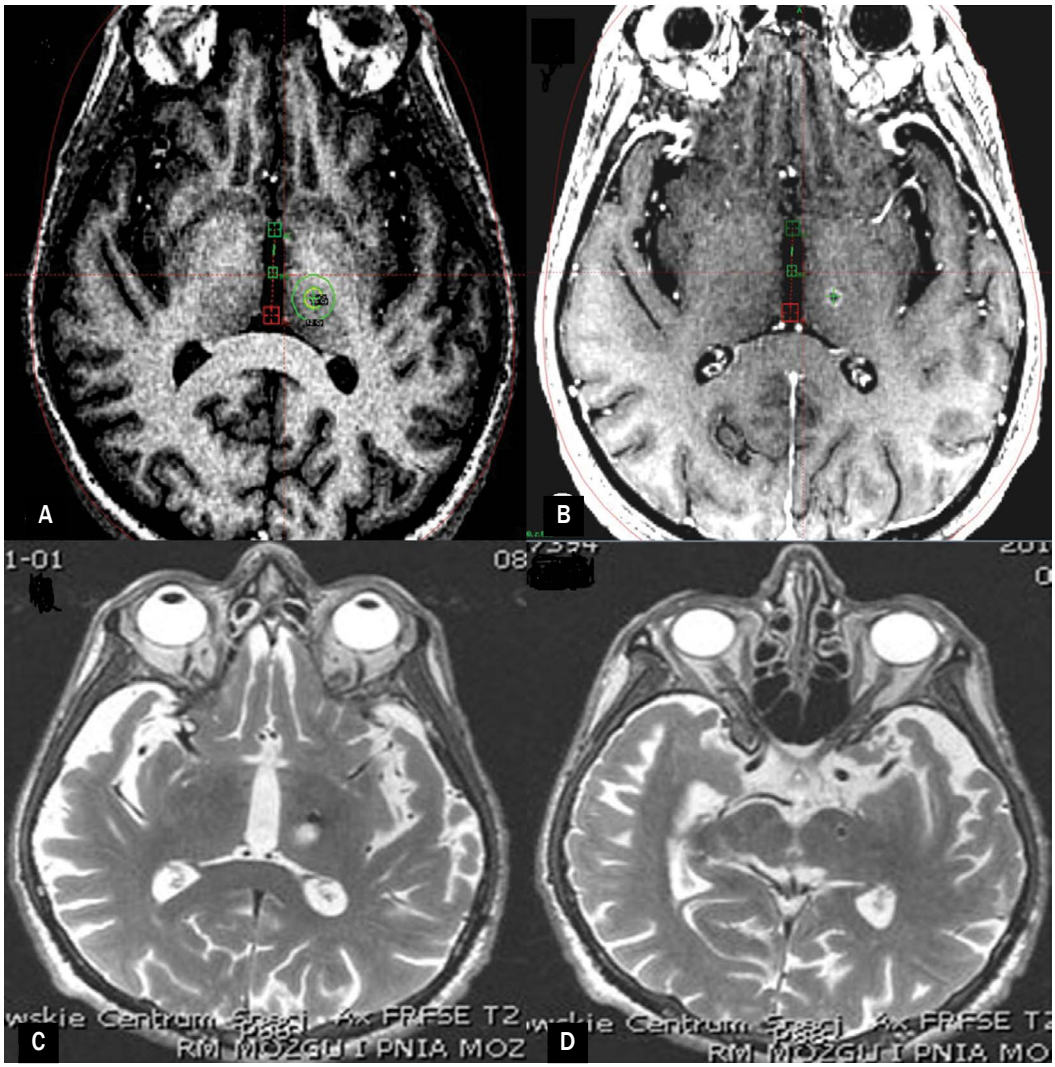

Figure 1. The Leksell Gamma Plan version 10 was applied to perform the left Vim gamma-knife thalamotomy. **A**) a 1.5 Tesla contrast--enhanced magnetic resonance images (MRI) were obtained to set the target coordinates using the Leksell Gamma Plan version 10. **B**) the postoperative contrast enhanced MRI performed 6 months after the radiosurgical Vim gamma-thalamotomy showed 6 x 6 mm lesion located in the left thalamus, **C**) the axial MRI shows the DBS lead anteriorly located to the largest diameter of left radiosurgical lesion. **D**) the axial MRI visualizes the contact 1 of St Jude's electrode in the left STN which was chosen for permanent stimulation

Following the administration of local anaesthesia, a stereotactic Leksell G head frame (Elekta Instrument AB, Stockholm, Sweden) was attached to the patient's head. DBS lead implantation was performed under local anaesthesia. The stereotactic STN planning adjusted to the patient's individual anatomy was done using direct magnetic resonance imaging targeted using a neuronavigation device (Stealth Station S7, Medtronic, Minneapolis, MN, USA) and software Framelink 4. He was on anti-platelet therapy due to his heart transplant and coronary disease with a stent placement. After obtaining cardiac consultation, the anti-platelet medication was stopped 10 days before the DBS procedure. Our patient was on a low dose of aspirin, taking only 75 mg once a day. He was given intra-venous unfractionated heparin using an initial bolus of 5,000 units two days before scheduled surgery. The partial thromboplastin time (APTT) was checked, with values ranging between 1.5 and 2.5. This was accomplished by checking the APTT again six hours after starting the infusion and adjusting the rate accordingly. The day before surgery the APTT was checked again. Moreover, the International Normalised Ratio (INR) was checked twice before surgery (48 hours and 24 hours before planned DBS procedure). If the INR was below 1.2 it was deemed safe to operate in this challenging patient. The unfractioned heparin was stopped 10 hours prior to surgery. The DBS procedure was uneventful. No microrecording was used and single pass for a permanent

DBS lead was used to decrease the possible incidence of haemorrhagic complications. Stereotactic computed tomography revealed proper lead placement without intracerebral haemorrhage. The patient was given unfractionated heparin for four days after surgery, and by day 5 the preoperative low-dose of anti-platelet therapy was recommenced. He was followed at our ambulatory clinic every six months and has been followed for 40 months since the DBS surgery. His MDS--UPDRS motor scores improved to 16, with no tremor in the right hand (motor score impacted by the untreated left body side). (Suppl. Video 1) Examination of the patient's hands showed visible deformities of the left hand with a so called striatal hand due to longstanding Parkinson's disease. (Suppl. Video 2) The right hand is free of such deformities. He is completely independent in performing daily living activities with his tremor-free right hand. Turning off the stimulation results in the reappearance of a right sided tremor. (Suppl. Video 3) The imaging of the patient's brain shows the DBS lead in relation to the gamma-knife induced lesion (Figure 1C) with the lead in the left STN (Figure 1D)

Here, we have presented, to the best of our knowledge, the first case of a patient who had a severe congestive cardiomyopathy who underwent previously successful heart transplantation, having had thereafter functional neurosurgical procedures to ameliorate his disabling PD tremor.

In general, patients on life-long anti-platelet or anti--coagulation therapy due to atrial fibrillation or valvular heart disease are considered to be at high risk of developing perioperative intracranial haemorrhage, and are not offered a DBS procedure. Some reports have highlighted the strict perioperative management necessary for those who undergo a DBS procedure and are on anti-platelet therapy [2]. Our patient also had a positive cardiac history and had been on anti-platelet therapy for nearly 10 years. He had an initially positive response to levodopa, but severe side effects caused by low blood pressure and a burning pain in the chest resulted in withdrawal of levodopa, levodopa agonists, and anticholinergic. He was first treated with a less invasive neurosurgical procedure, mainly Vim GKT rather than a DBS procedure. Because of persistent and incapacitating symptoms, he was subsequently successfully treated with a DBS procedure.

A literature review revealed only three papers reporting the application of DBS in patients after unsatisfactory GKT, and none of these patients had had heart transplantation [3–5]. Terao et al. described a 64 year-old woman with PD and severe resting tremor that was not completely abolished by right-sided GKT [3]. A similar report describing the feasibility of DBS after the previous GKT was published by Tuleasca et al. [4]. Finally, an interesting case of ventroposteromedial thalamic nucleus DBS was presented by Yamgoue et al. in the treatment of a recurrent facial pain [5].

The above mentioned cases, and our described case, highlight the observation that a neuromodulation procedure can be effective after failure of Vim GKT.

Acknowledgement

The patient signed a written informed consent for filming and posting it on line. The patient also agreed to be the subject of scientific observation and of scientific publication.

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