MEDICAL UNIVERSITY OF GDAŃSK

EUROPEAN JOURNAL OF TRANSLATIONAL AND CLINICAL MEDICINE

e-ISSN 2657-3156 2019 Vol. 2 No. 1 www.ejtcm.gumed.edu.pl

EUROPEAN JOURNAL OF TRANSLATIONAL AND CLINICAL MEDICINE

Photo on the cover by Agata Ewa Kaczyńska

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Publisher

Medical University of Gdańsk
M. Skłodowskiej-Curie 3 A
80-210 Gdańsk, Poland

Gdańsk 2019
e-ISSN 2657-3156

Online editon is the original version of the journal

2019 Vol. 2 No. 1

EUROPEAN JOURNAL OF TRANSLATIONAL
AND CLINICAL MEDICINE 2019;2(1):1-96

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AND CLINICAL MEDICINE 2019;2(1):7-22

INVITED REVIEW ARTICLE

Multiple sclerosis – new therapeutic directions

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Abstract

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease which affects the central nervous system. Currently, there are numerous disease-modifying therapies for this condition. Most of them address the inflammatory aspects of the disease and are most effective in the relapsing-remitting stages of multiple sclerosis. However, none of them can completely stop the progression of MS and they are usually associated with adverse effects. There is an ongoing search for novel approaches that involve different modes of action. Here, we discuss examples of new immunomodulating agents such as antigen-specific therapies, neuroprotectants, regenerative strategies and gut microbiota modification.

Keywords: multiple sclerosis • neuroprotection • novel therapies • remyelination • gut microbiome

Citation

Łowiec P, Trzonkowski P, Chwojnicki K. Multiple sclerosis – new therapeutic directions.
Eur J Transl Clin Med. 2019;2(1):7-22.
DOI: 10.31373/ejtcm/109612

Introduction

Multiple sclerosis (MS) is a chronic, autoimmune, demyelinating inflammatory and neurodegenerative disease that involves the central nervous system (CNS). It most commonly affects people between 20 and 40 years of age, predominantly women and it is a major cause of neurological disability among young adults. Most individuals with MS (85%) experience relapses-remissions during which rapid neurological worsening is followed by subsequent resolution of the symptoms. Unfortunately, after approximately 5-20 years the disease evolves into secondary-progressive phase, where the acute exacerbations are less frequent but there is a gradual neurological worsening overtime. A minority of patients develop a primary-progressive course of MS, with a constant increase in disability from the onset with no noticeable relapses [1].

MS has a multifactorial and complex pathogenesis with genetic and environmental factors involved [2-3]. The inflammation in CNS is driven by adaptive and innate immune system components [4]. Moreover, the-

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No external funds.

Available online: www.ejtcm.gumed.edu.pl

re is a dysfunction of T-regulatory cells in people with MS. It is thought that peripheral failure of tolerance facilitates auto-reactive T-cell activation, possibly by an infectious agent through a mechanism of molecular mimicry. Although MOG, MBP, PLP and other molecules have been suggested, initiating target of the immune attack is still unknown. T-helper cells are shifted towards disease-promoting Th1 and Th17 populations and B-lymphocytes also take a part in MS pathology [5-6]. Destruction of myelin reveals new, previously sequestered neuroantigens, which become a target for the immune system, perpetuating continuous destruction in the CNS [7]. As the disease progresses there is less and less inflammatory activity. Patients still accumulate disability through gradual axonal loss due to neurodegeneration that dominates in the progressive phase of MS. Factors such as mitochondrial dysfunction, oxidative stress, intracellular ion imbalance, microglia activation may contribute to that process.

Currently, none of the available disease-modifying drugs (DMDs) arrest completely the disease or can be considered fully curative. Most of these therapies are immunosuppressive and turn down immune responses without appropriate specificity towards defined disease-associated autoantigens. Thus, novel therapies involve selective approaches that promise to affect only auto-reactive processes specific to MS [1]. This could not only enhance efficacy, but also reduce side effects. Many problems still persist in reestablishing immunotolerance such as route of administration of therapeutic agents, optimal dose and distribution to the CNS. Current options in progressive MS are limited because available therapies address mainly the inflammatory aspect of the disease. They do not concentrate on halting neurodegeneration nor do they aim to regenerate neural tissue that is already lost. Thus, there is an ongoing search for novel therapies. Here, some of the current strategies will be highlighted.

Antigen specific approaches

Transderamal Myelin Antigens

A promising approach is concentrated on induction of tolerance to specific auto-antigens by applying transdermal patches saturated with a mixture of myelin peptides: MOG 35-55 (myelin oligodendrocyte glycoprotein), MBP 85-99 (myelin basic protein) and PLP 139-151 (proteolipid protein) [8]. Patients with relapsing-remitting MS (RRMS) have been observed and compared to placebo. The treated individuals, have shown slower disability progression, less lesion accumulation and lower relapse rate [9]. Myelin peptides, administered at doses of 1mg and 10 mg transdermally, have induced a specific population of dendritic cells in the skin and local lymph nodes and promoted generation of Tr1 regulatory T-cells. As a result, weakened myelin-related immune responses have been observed. Transdermal treatment has caused an increase in IL-10 with concomitant decrease in TGF-beta and IF-N-y secretion. Interestingly, the therapy did not affect the percentage of CD4+CD25+FoxP3+T-reg population [8]. Administration of transdermal myelin antigens proved to be safe with only mild local irritation of the skin reported [9].

Tolerogenic Dendritic Cells

Dendritic cells (DCs), not only process, present antigens and activate immune responses, but are also implied in tolerance induction. The main subpopulations of these cells are myeloid and plasmocytoid dendritic cells. Depending on the surrounding environment and maturation level they can be divided into immunogenic and tolerogenic. Tol-DCs are thought to induce tolerance via T-cells promoting their deletion, anergy or inducing a regulatory phenotype [10]. This knowledge has been translated into studies in animal model of MS called experimental autoimmune encephalitis (EAE). In these trials introduction of Tol-DCs coupled with myelin oligodendrocyte glycoprotein (MOG) has protected from induction or suppressed activity of the disease [11-13]. In one study Tol-DCs generated from RRMS patients and coupled with PLP induced selective hyporesponsiveness in autoreactive T-cells in-vitro [14]. Further trials are needed to asses feasibility of this approach in-vivo. Selective tuning of immune responses offers a lesser risk of adverse effects and perhaps greater efficacy. There are remaining questions about the best route of administration and selection of suitable myelin antigens in future studies that would apply tolerogenic dendritic cells [15].

Autologous Myelin-Coupled PBMCs

In ETIMS trial, induction of tolerance has been achieved through infusion of autologous peripheral blood mononuclear cells (PBMCs) coupled with selected myelin peptides in a group of RRMS and secondary progressive MS (SPMS) patients [16]. Similar approach has been proven in experimental autoimmune encephalitis with amelioration of the disease in terms of occurrence and severity of relapses [17]. In the aforementioned human study, patients who have shown in-vitro responses to one of the seven epitopes of MOG, MBP and PLP have been enrolled. PBMCs were

collected through leukapheresis and attached chemically to myelin peptides. Then, they were mixed with autologous plasma and administered intravenously to the patients. Participants were divided into two groups, one with low and the second- with high disease activity. They received escalating doses of the product. Reduction of specific T-cell responses to auto-antigens has been reported in the higher dose group. The proposed mode of action is thought to be induction of anergy to specific autoreactive T-cells, apoptosis of coupled cells and subsequent phagocytosis by APCs expressing IL-10 and PD-L1 [17-19]. Induction of regulatory cells has been indicated, but only a slight increase has been measured. Importantly, no elevation in Th1 and Th17 populations has occurred, with treatment being generally safe.

DNA and Peptide-based vaccination

An approach where a modified DNA encoding altered human myelin-basic protein (MBP) altered with less immunologically stimulating motifs has been explored as a therapeutic vaccine [20-21]. In this case, it was administered intramuscularly in a cohort of SPMS and RRMS patients. Reduction of newly forming lesions was observed, but with no substantial effect on clinical progression. In response to vaccination, less IFN-y secreting T-cells were produced and the levels of myelin-specific antibodies in the cerebrospinal fluid (CSF) decreased. Treatment was generally safe with no serious side effects. In another study, rather than DNA, introduction of TCR peptides from specific autoreactive T-cell clones has been used as a strategy [22-23]. They were administered either by intramuscular or intradermal route with addition of adjuvants to boost immunogenicity. The vaccine induced a subset of T-cells with subsequent reduction of responses to encephalitogens and secretion of IL-10 by these cells. Other proposed mechanism is related to an increased expression of FoxP3 in natural and inducible populations of T-regulatory cells [24]. Different approach used apitopes or short soluble peptides derived from naturally occurring MBP, which mimic processed epitopes [25-26]. After intradermal injection, they are bound to MHC-class II receptors on immature dendritic cells and are thought to induce specific T-regs. Risk profile was low. The therapy was safe with local skin reactions observed in a group of patients. Another trial [27] used mannosylatedlyposomes (CD-206) to facilitate re-uptake of immunodominant MBP peptides by dendritic cells which in turn should promote tolerance [28].

Not all efforts in peptide vaccination proved to be safe. Fear of disease exacerbation must be taken into account as evidenced by clinical worsening in patients who received altered MBP peptide ligand delivered subcutaneously [29].

Attenuated Autologous T-cells

A different cell vaccination technique involved the irradiation of myelin-autoreactive T-cells selected to be specific towards MBP, collected from the peripheral blood of individuals with RRMS and SPMS [30]. After that, autologous cells were reintroduced to the patients. A reduction of clinical and radiological activity of the disease was observed. The probable mode of action was an induction of specific cytotoxic T-cells against irradiated auto-reactive clones, which results in their deletion and selective suppression of autoimmune responses. Treatment has been safe with no general immunosuppression. Other trials with attenuated auto-reactive T-cells have been performed [31-33] with a wider repertoire of T-cells, auto-reactive not only to MBP. As in the first case, there were no serious adverse reactions.

Regenerative therapies

Prior therapeutic approaches targeted inflammatory processes that ultimately lead to demyelination and axonal loss. However, none of the above addressed possibilities of reversing the damage inflicted to the CNS during the course of MS. One avenue of research explores inhibition of molecules that contribute to myelin development suppression. LINGO-1 and AMIGO-3 are proteins which regulate neuroplasticity. LINGO-1 (Leucine-rich repeat and immunoglobulin-like domain-containing Nogo receptor-interacting protein 1) halts neurite outgrowth and mediates inhibitory effects on oligodendrocyte precursor maturation and therefore prevents axonal myelination. Other identified protein, AMIGO-3 (amphoterin-induced gene and open reading frame-3) exerts similar inhibitory effects as LINGO-1 [34]. Experimental blockage of LINGO-1 mediated signaling has shown benefits in animal models of CNS demyelination [35-36]. Human clinical studies gave mixed results. In the RENEW trial, Opicinumab (Li81 BIIB033) an anti-LINGO-1 antibody were used to treat acute optic neuritis. Some benefits were observed in patients assessed with multifocal visual-evoked potential (MF-VEP) measurement [37-38]. Furthermore, the antibody was tested in the SYNERGY study, where its safety profile and influence on disability was compared to interferon-β therapy in SPMS and RRMS. Primary endpoint of the trial was not met. However, modest positive results with good risk profile were observed in intermediate dose subgroups [39-40].

Limited results from above studies could be explained by other mechanisms compensating for the loss of function by LINGO-1, therefore other therapeutic

targets are sought [34]. Another discovery are natural antibodies (NAbs) directed towards CNS antigens and their remyelination-promoting subgroup [41-42]. One of them, rHIgM22 or recombinant human monoclonal IgM antibody-22, was used in EAE with positive effect on lesion load reduction and remyelination. Studies have shown that this antibody crosses the blood-brain barrier and exerts its effects without immunomodulation. It activates a signaling complex on oligodendrocyte precursor cells promoting their survival [43]. Presently, there are ongoing trials in MS, demonstrating its safe risk profile [44-45]. Other candidate for CNS repair is rHIgM12, reactive towards gangliosides and polisialic acid on neuronal surface, which promotes axonal growth [46]. Well known hormone, erythropoietin, induces remyelination and neuronal growth beyond its primary effects [47]. Although clinical benefit in small studies has been reported, larger trials have not proven efficacy in progressive MS [48-50].

Another approach is associated with multiple sclerosis-associated retrovirus (MSRV), which is a latent, endogenous virus, integrated into the genome. It can be reactivated in the course of EBV infection and the envelope protein (MSRV-env) has been found in CNS lesions of MS patients. As a Toll-like receptor-4 an agonist, MSRV-env has been shown to have proinflammatory properties, preventing remyelination by inhibition of oligodendrocyte maturation [51]. GNbAC1 is a monoclonal antibody engineered to bind the envelope protein which indirectly suppresses neuroinflammation and favors myelin deposition. CHANGE-MS trial in RRMS [52] supports GNbAC1 effects on remyelination [53-55]. Small molecules could also have similar capabilities. Domperidone, a dopamine receptor antagonist, is being tested in SPMS patients as prolactin released secondary to dopamine blockade, could improve remyelination [56-58].

Novel monoclonal antibodies targeting the immune system

Immune cell targeting monoclonal antibodies

Rituximab is not officially approved for the treatment of MS, but this anti-CD20 chimeric monoclonal antibody is used off-label and has shown efficacy in remitting-relapsing forms of the disease. It reduces the annual relapse rate (ARR) and risk of enlarging T2 MRI lesions in comparison to placebo as shown in HERMES trial. Its mechanism of action is similar to ocrelizumab and it is thought to be depletion of circulating B-cells and CD20-bearing T-cells.

Ocrelizumab has been approved in 2017 for the treatment of MS. This anti-CD20 monoclonal antibody is a breakthrough, because it is the first type of treatment that has been proven to show benefit in individuals with the primary progressive form of MS.

The success of monoclonal antibodies such as ocrelizumab and rituximab has led to further search for drugs with similar pharmacodynamics. Ofatumumab, an anti-CD20 humanized antibody, has been used in the treatment of chronic lymphocytic leukemia and rheumatoid arthritis [59-60]. As compared to rituximab, it binds to a different epitope resulting in a more pronounced complement-dependent cytotoxicity due to slower dissociation from the targeted antigen. As a result, profound B-cell depletion is noted. In phase II trial, ofatumumab has been administered intravenously to RRMS patients, with no increased risk of severe infections [61]. Ofatumumab has shown efficacy in reducing MRI markers of disease activity. Another placebo-controlled trial in RRMS patients explored a subcutaneous route of administration with good tolerance and comparable neuroimaging results [62].

Inebilizumab (MEDI-551) is a monoclonal antibody targeting CD19 receptor. It causes a rapid B-cell depletion similarly to the therapies directed against CD20(+) cells and immunologically translates to comparable effects. RRMS patients in phase I study, had slower lesion accumulation and acceptable risk [63]. BAFF or B-cell activating factor is a protein found both on B-lymphocyte membranes and in an unbound form. Its main function is a promotion of B-cell activation and survival. Located mainly on mature B-cells, BAFF is a target for tabalumab. Tested in patients with SLE and rheumatoid arthritis, it has shown effects on biological markers but with no clinical benefit. Acknowledging the role of B-cell mediated pathology in MS, tabalumab has been investigated as an option for patients with RRMS in a trial focused on safety and radiological activity markers, although with no reduction in new gadolinium-enhancing lesion formation [64].

Cytokine targeting monoclonal antibodies

The role of IL-17 and IL-12 has been implied in the pathophysiology of MS. T-lymphocytes that undergo differentiation to a Th17-phenotype are linked to neuroinflammation as their concentration correlates with disease severity in EAE. IL-17 activates microglia, macrophages and astrocytes, which secrete cytokines such as IL-6, TNF-a, IL-1 which in turn increase blood-brain barrier permeability and recruit more immune cells into the CNS. Enhanced myelin destruction and axonal loss occurs as a result [65]. IL-12 secreted by APCs in the CNS activates macrophages, B-cells, Th1

cells and promotes inflammation. As in the periphery, this cytokine together with IL-23 differentiate naive T-cells into a Th17-subtype.

Ustekinumab is a monoclonal antibody targeted against the p40 subunit of IL-23 and IL-12 cytokines [66]. Studies using the EAE model have shown reduction in disease severity, however its efficacy has not been supported in human trials [67-69]. This discrepancy could be explained by low fraction of antibodies crossing the BBB, non-dependence from IL-23 signaling and disease compartmentalization to the CNS in the later stages of MS [70].

Secunikumab, a monoclonal antibody specific to IL-17A, aims to block the effects of this cytokine. Selective targeting of this interleukin is more beneficial than suppression of Th17 cells, because IL-17 can be secreted independently by δγT cells, astrocytes and oligodendrocytes in the CNS. There is the evidence that it could reduce radiological activity in patients with RRMS [71]. Risk of adverse effects has been acceptable with higher incidence of infections.

Tocilizumab approved for the treatment of resistant rheumatoid arthritis, is an antibody directed against IL-6, which promotes differentiation of naive T-cells towards Th17 subtype [72]. Blockage of this signaling has prevented the development of EAE. Unfortunately, tocilizumab has been associated with cases of new-onset MS in patients receiving the antibody for other indications, which raises concerns about its safety profile [73].

Aside from its proliferative properties, GM-CSF activates and recruits myeloid cells to the CNS during neuroinflammation and promotes their maturation [74]. MOR103 is a monoclonal antibody that interferes with GM-CSF on coupling to its receptor. As subsets of B-cells produce GM-CSF and contribute to MS pathology [75], MOR103 has become a potential treatment option in MS and recent trials have shown good tolerance of this drug [76].

Neuroprotectants

Ion-channel blockers

Experimental evidence has shown that the accumulation of sodium ions may lead to an increased intracellular calcium concentration. This activates signaling that can cause cell death. This mechanism can be referred to the neuronal loss seen in MS patients [77-78]. Ion channel blockade can reduce influx of sodium and thus lead to neuroprotection. Many antiepileptic drugs act as sodium-channel blockers and are being explored as a treatment in MS. Lamotrigine has been investigated in trials as a neuroprotectant with mixed results [79]. One study has not shown efficacy in reducing serum neurofilament concentrations in patients receiving lamotrigine, although subgroup analysis has suggested some benefit [80]. Phenytoin administered in acute optic neuritis has had a positive effect on retinal nerve fiber thickness measured using OCT [81]. Another trial using the EAE model supports the efficacy of oxcarbamazepine [82]. It has been studied in SPMS patients in order to explore its neuroprotective properties (NCT02104661). Riluzole, a tetradotoxin-gated sodium channel blocker, is being tested in hope that it could prevent neurodegeneration in MS [83-84]. Further developments are ongoing as other agents share similar mode of action [85]. Amiloride, an acid-sensing sodium ion channel blocker, has been explored as a treatment in SPMS [83]. However, results in optic neuritis have been unsatisfactory [86].

Inhibitors of microglia activation

Microglial cells as a part of the innate immune system are thought to participate in destructive processes in the course of MS. Fluoxetine, aside from its antidepressant activity, also acts as a blocker of microglial-mediated inflammation. Furthermore, it has other beneficial effects such as up-regulating the expression of BDNF [87-88].

Laquinimod, which has undergone phase III trials, has not shown slower disability progression in lower doses (CONCERTO trial) in RRMS patients. Moreover, higher doses have been linked to unacceptable risk of cardiovascular events. Clinical studies in PPMS gave unsatisfactory results [89-90]. Pretreatment as well as administration in developed EAE caused reduced demyelination. Spinal cords and optic nerves of treated mice were infiltrated by phagocytes to a lesser extent in laquinimod treated groups. Human immune cells treated in-vitro also displayed decreased activation, thus suggesting the role of this mechanism in neurodegeneration [91-93].

Minocycline, an oral antibiotic from the tetracycline family, beyond antimicrobial activity, also exerts anti-inflammatory effects. It inhibits NMDA-mediated microglia activation in-vitro and it also promotes alternate anti-inflammatory differentiation of these cells in animal models of post-stroke neuroinflammation [94-95]. These effects could also be explored in MS and one study has shown a reduced risk of transformation from CIS to MS [96].

Ibudilast, an phosphodiesterase inhibitor, is a small molecule that crosses the blood-brain barrier. It acts as a neuroprotectant by inhibiting microglia activation

and antagonism of macrophage-migration inhibitory factor. Furthermore, it also induces neurotrophin secretion [97-98]. In phase II trial ibudilast has exhibited efficacy in slowing down brain atrophy in patients with progressive MS [99].

Antioxidants and agents improving mitochondrial function

Disruption of energy production and dysfunction of mitochondria has been already implied as a contributing factor for neurodegeneration which takes place in MS. Increased demand for ATP in demyelinated axons with insufficient production of ATP by mitochondria can lead to intracellular sodium accumulation and secondary influx of calcium ions that promotes cell death [100-102]. Biotin is essential for energy homeostasis as it functions as a co-factor for essential enzymes catalysing carboxylation. These are involved in lipid synthesis, amino acid metabolism and Krebs cycle. Administration of high oral doses has slowed and, in some cases, reversed disability progression in patients with progressive MS. Beneficial effect on visual acuity has been reported in MS patients with progressive optic neuropathy. It probably promotes remyelination and mitochondrial energy production [103-105]. Biotin-dependent acetyl-CoA carboxylase catalyses the synthesis of malonyl-CoA, a substrate for production of fatty acids and thus, promotes myelin deposition. Furthermore, it may provide substrates for the Krebs cycle and raise levels of intracellular ATP.

Idebenone, an ubiquinone analogue, also functions as an electron carrier in oxidative phosphorylation. Trials with this agent gave positive but disputable results in Leber's hereditary optic neuropathy [106] and Friedreich's ataxia, genetic diseases where mitochondrial dysfunction has been reported [107-108]. The antioxidant has been explored as a neuroprotectant in EAE, although recent studies have yielded unfavorable results. Nevertheless, idebenone has been investigated as a treatment for MS [109].

Another free radical scavenger, MitoQ consists of triphentylphophonium lipophilic cation attached to an alkyl chain linked with ubiquinone that enables it to be efficiently up-taken by mitochondria. It exerts its antioxidative effects by aiding mitochondrial function [110]. Administration has been protective against neuroinflammation and axonal degeneration in mice with induced EAE.

Alpha-lipoic acid, a natural molecule, has also potent antioxidative effects [111]. This endogenous molecule exerts neuroprotection via regeneration of glutathione pool, neutralization of free radicals and aids oxidative phosphorylation as a co-factor of pyruvate dehydrogenase. Interestingly, it also inhibits leukocyte migration to the CNS. Alpha-lipoic acid has reduced MMP-9 and sI-CAM concentrations with positive effects on blood-brain barrier integrity and reduction of brain atrophy in a small cohort of SPMS patients [112-113].

Neuroprotective agents with other modes of action

Simvastatin, the statin noted for its protective effects on vasculature, has pleiotropic effects aside from suppression of cholesterol synthesis. It is also known for its immunomodulatory effects [114]. It has been investigated in SPMS as a disease-modifying drug in MS-STAT study. Improvement on the quality of life and cognition in patients receiving high-dose simvastatin has been reported and the rate of brain atrophy has been reduced [115-116]. These neuroprotective effects could be explained by a combination of positive effects on cerebral blood flow and anti-oxidative properties [117-118]. Further trials are needed to assess feasibility of simvastatin in MS.

Siponimod, closely related to fingolimod, is another immunomodulatory agent. It has a similar mode of action as it affects recirculation of lymphocytes from the lymph nodes. It improves over fingolimod as it is more selective towards S1P and S5P receptors. It has been shown to slow disability progression. Siponimod administration resulted in a reduction of brain atrophy in individuals with SPMS suggesting neuroprotective effects exerted by modulation of S1P and S5P receptors that may mediate brain cell survival. Adverse reactions are similar to fingolimod [119-120].

The role of glycogen synthase kinase-3 (GSK-3) is suggested in immune response regulation [121]. Lithium, a treatment for bi-polar disorder, suppresses the function of the enzyme and has caused prevention of EAE onset and disease amelioration [122]. A trial in progressive MS has been performed to study effects on brain atrophy and evaluate lithium's neuroprotective effects [123].

Gut microbiome modification

A complex community of microorganisms that inhabit the gastrointestinal tract is often referred to as the gut microbiome. Its influence on the nervous system has been more highlighted recently as it exerts its effects through immunological, endocrine and direct neural mechanisms [124]. The metabolites produced by intestinal bacteria such as short-chain fatty acids (SCFAs), sustain blood-brain barrier integrity, induce T-reg populations and regulate function of microglia in

the CNS. Polisaccharide-A, a metabolite of Bacteroides fragilis, has been reported as an immunomodulatory factor. Furthermore, stress-mediated hypothalamic-pituitary axis activation can lead to changes in intestinal barrier permeability and dysbiosis through actions of glucocorticosteroids and catecholamines. Involvement of neural pathways between the digestive tract and the CNS is important. Bacteria in the gut may interact with afferent neural fibers by producing neurotransmiters and directly stimulate them with their molecular patterns. In addition, stimulation of efferent signaling nerves can regulate immune cell activity [125]. The role of this gut-brain axis has been implied in pathophysiology of psychiatric and neurological disorders such as MS [126].

Immunomodulatory effects caused by microbiome modification either by antibiotic treatment or probiotics can be supported by evidence from animal models [127-129]. In one study, the incidence of EAE was higher in genetically prone mice with gut microbiome transplanted from MS affected subjects [130]. There are also hints that people with MS have a distinct composition of gut flora [131]. Moreover, besides blood-brain barrier, the intestinal barrier is also disrupted in many patients with MS and it may contribute to pathology of the disease. Gut flora can affect bile acid composition and vice-versa. Thus, strategies to modify the gut microbiome have been formulated. Trials in EAE in which probiotics were used have shown efficacy [132]. There is a possibility that such microbiological interventions could be translated to patients with MS as there are results from human studies that support such approaches. For example, there are ongoing trials with fecal microbial transplantation (FMT) [133-135]. Therapeutical infestation with helminths has been also explored, because parasites are been known to skew immune response towards Th2 subtype, thus in effect ameliorating neuroinflammation [136-138].

Conclusions

Currently there is a variety of treatments available for patients with multiple sclerosis and this number is rising. They can be divided into symptomatic drugs (used in the setting of a relapse, e.g. glucocorticoids and IVIG) and disease-modifying drugs (DMD) that aim to influence long-term progression of the disease. None of aforementioned therapies are fully curative and most of them affect relapsing-remitting forms of the disease. Search for more specific therapies is ongoing that either try to reestablish self-tolerance, concentrate on regeneration and neuroprotection or modulate innate immune responses that are prominent in later stages of the disease and therefore promise a safer and hopefully more effective treatment in the future.

Conflicts of interest

None.

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EUROPEAN JOURNAL OF TRANSLATIONAL
AND CLINICAL MEDICINE 2019;2(1):22-27

RESEARCH ARTICLE

Statistical methods for the assessment of students' knowledge as illustrated by the Introduction to Internal Medicine exam

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Abstract

Background: We wanted to develop substantial and statistical methodology for complex assessment of quality of teaching internal medicine in medical university. Our aim was also to check connection between the results obtained during the midterm and final exam. **Materials and methods:** We have compared the results obtained by Polish (n=235) and English Divisions (n=81) students achieved during the midterm exam and multiple-choice final exam. The mean scores were calculated with t-Student test. For further evaluation Wilcoxon tests were used with the Bonferroni correction, The Stuart-Maxwell test was carried out to verify the hypothesis about correlations between results in the midterm and final exam. **Results:** The mean midterm exam score was 84.4% in PD and 72.6% in ED ($p < 0.0001$) and mean final exam score was respectively 72.3% and 55.6% ($p < 0.0001$). Good result of the final exam was obtained by 62% of students who passed well the midterm exam. **Conclusions:** It is crucial to use appropriate tools to grade the quality of tutorship. To evaluate that one should use advance statistical tests. The fact that ED students achieve less points on the exams might have few reasons like a language barrier. Obtaining a good result during midterm exam does not guarantee passing the final exam.

Keywords: exam evaluation • statistical methodology • Iinternal medicine

Citation

Stefański AI, Bladowska N, Więczkowska A, Wojtyniak B, Ignaszewska-Wyrzykowska A, Jasiel-Wojculewicz H, Jendrzejewski J, Rutkowski M, Zdrojewski T, et al. Statistical methods for the assessment of students' knowledge as illustrated by the Introduction to Internal Medicine exam. Eur J Transl Clin Med. 2019;2(1):22-27.
DOI: 10.31373/ejtcm/105493

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No external funds.
Available online: www.ejtcm.gumed.edu.pl

Introduction

For several years, increasing attention has been paid to improving the quality of teaching at universities, also in Poland. During this time, several initiatives were aimed at systemic improvement of the teaching model. One of the effects of these efforts was the introduction of the National Qualifications Framework, which includes the development of teaching standards for universities. Currently, the curricula are based on demonstrating the potential for student to acquire and consolidate knowledge, skills and competences related to the particular subject. Despite the unquestionable value of the new standards, they were criticized for listing far too detailed teaching goals, the need to verify skills and competencies, especially at general universities where the basic goal is to acquire knowledge [1-3]. This is less of an issue in higher vocational schools where gaining professional skills and competencies to perform a specific profession are equally important as the acquired knowledge. Medical university curricula are developed taking into account a set of requirements and learning outcomes [4].

In accordance with the Act of 20 July 2018 on the Law on Higher Education and Science, the Minister of Science and Higher Education in consultation with the Minister of Health issued a regulation defining unified educational standards. The current legal act is the Ministerial Announcement dated 9 January 2018, which specifies in detail the required learning outcomes divided into knowledge and skills in the field of morphological, pre-clinical, behavioral, clinical surgical and non-surgical sciences and the related legal aspects [5-6]. In addition, this regulation highlights the various methods that can be used to evaluate the pre-defined learning outcomes. Students' knowledge can be evaluated by oral or written exams. Types of written exams assessing knowledge include written essays and reports, open-ended questions, multiple-choice tests (single-select questions, multiple-select questions, true/false questions and matching questions).

Multiple-choice (often described as 'objective exams') became a commonly used tool to assess students' knowledge at various levels of their education, including medical universities. This is a quite effective method to check the scope and depth of knowledge acquired by students. Furthermore, such tests also indirectly assess the effectiveness of teaching. Multiple-choice tests are considered the fairest way to verify the level of mastery of the material, because all students are evaluated anonymously, in the same reproducible way, and the result does not depend in any way on the examiner [7]. An additional advantage of this form of assessment is the fact that many students can take this exam simultaneously and yet the results can be an-nounced in a very short time thanks to a properly prepared answer sheet and its computer evaluation, limiting the possibility of human error and bias while checking the test [8]. Addi-tionally, the multiple-choice test format makes it easy to gather data for further evaluation of the test itself, the individual questions or the level of mastery of the material to which the questions referred. Using adequate statistical tools could help to verify which parts of in-structed material need further verification so that teacher could concentrate more on these subjects. The multichoice tests were introduced in the Department of Prevention and Didac-tics of the Medical University of Gdańsk twenty years ago and since then they have been in-creasing the quality of the knowledge assessment of our students [9-10].

Medical didactics is a field that is currently undergoing rapid development. Therefore, proper evaluation methods are needed. Unfortunately, there are few statistical methods in the available literature that would meet the objectives. Teaching a vast subject such as internal medicine is one of the main tasks of all medical schools and a challenge for medical teachers. Therefore, it is necessary to effectively and transparently monitor students' knowledge and achievements. The aim of our work was to develop a methodology for assessing and comparing the results of exams assessing knowledge of third-year students of the Polish and English Divisions acquired during the Introduction to Internal Medicine 2 course.

Materials and methods

Study definitions

The Introduction to Internal Medicine 2 course is included in the third-year curriculum of the Medical Faculty for both the Polish and English Divisions. The course includes 15 hours of seminars and 50 hours of bedside classes. In the second week of the spring semester students write a theoretical (open questions) and a practical midterm exam (whose results were not included in this analysis). The year-long course ends with a multiple-choice final exam.

Theoretical midterm exam

In the academic year 2016/2017, 233 students of the Polish Division (PD) and 80 students of the English Division (ED) wrote the theoretical midterm exam. The theoretical midterm exam conducted in the middle of the course consisted of 7 open questions with identical or similar content and level of difficulty (see

Appendix No. 1). Topics covered the symptomatology of basic cardiovascular, respiratory and digestive diseases discussed in classes so far. The questions were based mainly on the symptoms evident when taking patient's history and performing physical examination during seminars and bedside classes (if relevant patients were available). A maximum of 22 points could be obtained on the midterm exam.

Appendix 1.

- What is a physiological lung sound upon auscultation? List four causes of diminished sound upon auscultation of the lung. / What is a physiological lung sound upon percussion? List four causes of dull sound upon percussion of the lung.
- How can you diagnose dehydration upon physical examination?
- What signs and symptoms could you find upon physical examination in a patient with pneumonia? / What signs and symptoms could you find upon chest examination of a patient with pneumonia?
- In which acquired valve pathologies you might find a diastolic murmur upon auscultation of the heart? / In which acquired valve pathologies you might find systolic murmur upon auscultation of the heart?
- What is Horner syndrome? Write its causes and list its symptoms
- List symptoms of chronic right ventricular failure. / List symptoms of chronic left ventricular failure.
- Draw a graph of: - hectic fever, - Cheyne-Stokes breathing. / Draw a graph of: - intermittent fever, - of Kussmaull's breathing.

Multiple-choice test

Two hundred and thirty-five students of the Polish Division and 81 students of the English Division took the final exam. It was a final test written by the same students that wrote the midterm exam (changes in number of students between both exams were due to illness-related absence). The multiple-choice test consisted of 100 questions of various types (single-select questions, multiple-select questions, questions with negation, premise-conclusion questions). Question content was the same for Polish and English Division students. Each question contained 5 answers to choose from. Students had 100 minutes to write the exam. Three versions of the test were prepared for each group, differing only in the order of the questions. The questions checked the knowledge acquired during the Introduction to Internal Medicine course in the field of cardiology (21 questions), pulmonology (8 questions), endocrinology (8 questions), gastroenterology (8 questions), nephrology (13 questions), hematology (6 questions) hypertension and diabetes (13 questions) and physical examination (23 questions).

Statistical analysis

The statistical analysis of the theoretical midterm exam results was performed with the t-Student test for independent variables. The mean scores of the multiple-choice test results obtained by students of the Polish and English Divisions were calculated and subjected to statistical analysis with the t-Student test.

Levels of questions regarding different areas of internal medicine were assessed by treating every student as an individual statistical unit and the thematic category in which he or she obtained the best result, i.e. the highest score, was determined and the number of the students' best results was summed up for each category. The analysis of related variables was performed using non-parametric Friedman's test and Wilcoxon's test with the Bonferroni correction; (P-value <0.05). A total of 28 Wilcoxon tests, using the Bonferroni correction that involves multiple repetitions in the same pool of data sets, were performed successively within the categories of questions from the final exam.

To check whether the students who did well on the theoretical midterm exam also passed the final exam, their exam results were divided into score subgroups: every 5% for Polish students and every 10% for ED students (due to much lower number of ED students). Since there was no linear relationship between the results of the midterm and the final exam, the students of both divisions were pooled into one group and the analysis was repeated following the calcu-lation of Pearson's correlation coefficient. Then, the results of the midterm exam and the final exam were divided into two levels: level 0 (0–59% of correct answers – exam failed) and level 1 (60–100 % of correct answers – exam passed). McNemar's test was performed (P-value <0.05), which rejected the null hypothesis that the proportions of passing scores is equal for both exams. In the next analysis, the results of the midterm and the final exam were divided into three levels: level 0 (0–59% of correct answers – exam failed), level 1 (60–69% of correct answers – exam passed poorly) and level 2 (70–100% of correct answers – exam passed well). The Stuart-Maxwell test was carried out and the P-value was <0.05.

Results

The mean midterm exam score was 84.4% among the PD students and 72.6% among the ED students (p <0.0001). The mean final exam score was 72.3% (71.4, 73.2) PD students and 55.6% (53.4, 57.8) among the ED students (p <0.0001). The exam was failed by 5 PD students (2.1%) and 32 ED Students (40%). The specific topics in which the students obtained the highest scores (percentage of students who had the highest results in this area) were hematology and gastroenterology (88% and 86%, respectively), followed by hypertension/diabetes and endocrinology (49% each), pulmonology, cardiology and nephrology (42%, 39% and 23%, respectively) and physical examination (the lowest score of 12%, see Table 1). The Wilcoxon's tests with the Bonferroni correction showed that categories of questions from endocrinology, pulmonology, cardiology and physical examination were answered similarly. After dividing the students into two groups depending on the score obtained (level 0: 0–59% of correct answers – exam failed and level 1: 60–100% of correct answers – exam passed), it was shown that among those who failed the midterm exam (overall 53 examinees in both divisions), 36 students (68%) did not pass the final exam, but only every third student who failed the midterm exam had positive grade on the final exam (17 students, 32%). Of all those who passed the midterm exam, 136 students (62% of examinees) succeed on the final exam (Table 2).

Analysis performed after dividing the students into three score levels (level 0: 0–59% of correct answers – exam failed, level 1: 60–69% of correct answers – exam passed poorly and level 2: 70–100% of correct answers – exam passed well), showed that good result of the final exam was obtained by 23 students (11%) who failed the midterm exam and 136 students (62%) who passed well the midterm exam (Table 3). Additionally, we analyzed if the PD students' final exam results were correlated with in terms of admission to the University. To clarify, we compared the students who were admitted to our University during primary enrollment (exceeded the required number of points scored on the secondary school exit exams) and those who were qualified during additional enrolment period (students who did not earn the points required for primary enrolment, they fully participate in all the classes but have to pay for tuition). The mean exam scores among those 2 groups were 72.5% and 70.1%, respectively (p = 0.04).

Table 1. Number of students whose highest scores were in the respective topics

Category	Quantity
Cardiology	39
Diabetes and hypertension	49
Endocrinology	49
Gastroenterology	86
Physical examination	12
Hematology	88
Nephrology	23
Pulmonology	42

Table 2. The results of the midterm exam and final multiple-choice test

		Final test	
		0	1
MIDTERM	0	**36** (68%)	**17** (32%)
	1	**83** (38%)	**136** (62%)
TOTAL		**119**	**153**

0 (0–59% of correct answers – exam failed),
1 (60–100 % of correct answers – exam passed)

Discussion

It is difficult to find well-designed and effective statistical methods in the available literature that can be used for evaluation of exam results beyond just comparing mean values8. Simple statistical methods allow establishing which group of students achieved better learning outcomes and whether the difference between the data is statistically significant. Howev-

Table 3. The results of the midterm exam and final multiple-choice test

		Final test		
		0	1	2
MIDTERM	0	**10** (44%)	**7** (30%)	**6** (26%)
	1	**10** (33%)	**9** (30%)	**11** (37%)
	2	**23** (11%)	**60** (27%)	**136** (62%)
TOTAL		**43**	**76**	**153**

0 (0–59% of correct answers – exam failed),
1 (60–69% of correct answers – exam passed poorly),
2 (70–100% of correct answers – exam passed well).

er they cannot for example determine whether the students who achieved good results on a written midterm exam also obtained high scores on the final multiple-choice test or to find which topics on the exam were the least and the most difficult. That is why we decided to development our own method for statistical evaluation in order to assess the results from various types of exams and to identify the topics on which greater emphasis should be placed in the teaching process.

Our analysis also compared the results obtained by students of the Polish and English Divisions who answered the same questions. In both the theoretical midterm exam and final multiple-choice test, students of the Polish Division obtained statistically significantly higher scores (84.4% vs 72.6% and 72.3% vs. 55.6%, respectively; p <0.0001 for both). This may be due to various factors, with the language barrier being probably the most important. PD students are taught and examined in Polish which is their native language, whereas the ED students have all their classes in English which for majority of them is their second or even third language. Therefore, it takes more time for them to study the same material. It is noteworthy that English is also the second language of the teachers who wrote the exam questions, which might have caused additional problems in understanding the meaning of some of the exam questions. This issue has been known for quite a long time. In 1975 Massam reported that 60% of foreign medical school graduates who applied to work in United Kingdom, failed the English language and professional competence test [11]. This shows that there might also be some differences in teaching standards between the various countries around the world. Obviously all medical teaching and tests are prepared based on the medico-legal demands of the country where the teaching takes place.

The results of students admitted to the University in primary and additional enrolment (explained above) were also evaluated and the difference in scores between the two groups was statistically significant (72.5% vs. 70.1%; p = 0.04). This might be explained by the fact that students who were admitted during the additional enrollment round might have had some shortages in knowledge from the beginning (since they have had worse results on the secondary school exit exams).

The analysis of student's results achieved during midterm and final exams showed that obtaining a good result on the theoretical midterm exam does not guarantee a high score on the final test exam. Perhaps some students who received a high score on the midterm exam did not study enough before the final exam. In contrast, some of the students who failed the midterm exam might have been more motivated to better prepare for the final exam.

It is very important to use appropriate tools to check the quality of teaching. To evaluate didactics in such a complex subjects like internal medicine one should not use simple statistical tests but those that include the fact that the same student answered questions from different fields of internal medicine (related variables). The most important achievement of our work is the development of statistical methods that enable the assessment of complex parameters describing student results achieved on multiple-choice tests or open-question exams. The prepared tools can be used to analyze various forms of the assessment of students' knowledge regardless of the course being taught.

Limitations of the study

This study compared the results obtained by Polish and English Division medical students during midterm and final exams. PD students answered the questions in Polish which is their native language, as opposed to ED students whose exams were written in English which is the second or even third language for majority of those students and the second language for the majority of the teachers. This issue might be a very important reason for the results that we obtained. Authors also understand that statistical methods described above might not be applicable to every type of the examination but could be used to asses similar types of exams.

Conclusions

It is important to use appropriate statistical tools to evaluate the quality of tutorship and to discover areas of presented material which needs more attention put both by students and teachers. There might be several reasons for the finding that ED obtained worse results on the exams, however the language barrier seems to be the main issue. The students who performed well on the midterm exam were less likely to fail the final exam.

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EUROPEAN JOURNAL OF TRANSLATIONAL
AND CLINICAL MEDICINE 2019;2(1):28-35

RESEARCH ARTICLE

Comparison of clinical and echocardiographic parameters in patients with hypertrophic cardiomyopathy older and younger than 60 years old

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Abstract

Background: Hypertrophic Cardiomyopathy (HCM) is one of the most common genetic myocardial diseases. Transthoracic echocardiography which includes speckle tracking technique is tool for HCM diagnosis and monitoring the course of the disease. The aim of this study was to compare clinical and echocardiographic parameters in HCM patients older and younger than 60 years old (yo). **Materials and methods:** We prospectively enrolled 53 HCM patients, who were divided into two groups: younger and older than 60 yo. Clinical parameters, standard echocardiographic indices, as well as strain parameters were assessed and compared between the groups. **Results:** The older subgroup was characterized by a higher prevalence of coronary artery disease. In the younger subgroup the incidence of atrial fibrillation was quite high, which occurs far more often than in the general population. Echocardiographic analysis showed worse diastolic function in older, as well as lower volume of the LV. The global longitudinal strain was worse in <60 patients. The 3D strain parameters differed significantly between the groups: the area and radial strains were worse in younger patients. **Conclusions:** HCM patients older and younger than 60 yo differ significantly in terms of clinical and echocardiographic parameters.
Keywords: hemorrhoids • internet • patient preference • google trends • search engine

Citation

Wabich E, Raczak G, Rozwadowska K, Zienciuk-Krajka A, Szymanowicz W, Kozłowski D, et al. Comparison of clinical and echocardiographic parameters in patients with hypertrophic cardiomyopathy under and over 60 years of age. Eur J Transl Clin Med. 2018;1(2):28-35.
DOI: 10.31373/ejtcm/99667

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No external funds.
Available online: www.ejtcm.gumed.edu.pl

Introduction

Hypertrophic Cardiomyopathy (HCM) is one of the most frequent genetic diseases, constituting up to 0,2% of general population [1]. In this medical condition the thickness of one or more segments of the left ventricular wall is ≥15 mm and it cannot be explained by the increased left ventricle load [2]. In 60% of adults, the disease is associated with mutations of the cardiac genes coding for sarcomere proteins [2]. Other reasons underlying the development of HCM include congenital metabolic disorders, neuromuscular diseases, mitochondrial diseases, congenital malformations, amyloidosis, drug-induced hypertrophy. However, in 25-30% of patients, the cause of HCM remains unknown. [2]

Transthoracic echocardiography is the most important tool for HCM diagnosis and checking the development of the disease. This method allows to determine the basic parameters describing HCM: hypertrophy of the left ventricular (LV) segments, left atrial (LA) enlargement and LV diastolic dysfunction, which are natural consequences of this disease. Currently available *speckle tracking technique* additionally allows a detailed assessment of segmental and global LV function [3-7]. This dynamically developing domain of echocardiography allows researchers to assess the function of the LV at very early, preclinical stage of the disease, when the left ventricle ejection fraction (LVEF), assessed by standard echocardiography, is usually preserved [8].

Most of the HCM population studies concern on young patients, before the age of 60. But only few concentrate on elderly patients [9-11], thus it should be emphasized that this is a group in which the HCM diagnosis is more frequent. This situation is most likely a consequence of the growing number of echocardiographic examinations in elderly people and the high availability of echocardiography [11]. Despite the wide availability of echocardiography, there are still no clearly defined guidelines for the management and risk stratification in elderly people with HCM [9-11]. In literature there is also no data concerning to a comparison of older and younger patients with HCM.

Aim

The aim of the present study was to compare clinical and echocardiographic parameters (by standard as well as *speckle tracking* echocardiography) in HCM persons older and younger than 60 years old.

Material and methods

Fifty three HCM patients were prospectively enrolled [2]. Exclusion criteria were: <18 years of age, with NYHA class IV heart failure, coronary or hemodynamic instability at the moment of enrollment, a history of hospitalization due to cardiological reasons within the 3 months prior to enrollment and poor clinical prognosis.

Echocardiography

Echocardiography was performed in every person (GE VIVID E9; probe M5S; offline analysis using EchoPAC). During the same examination, 3D datasets were obtained in apical view using a matrix-array 3D transducer (4V). Standard echocardiographic parameters were measured according to relevant guidelines [12-14].

Standard echocardiographic parameters

The LA anterior-posterior size (LADs), LV end-diastolic diameters (LVEDD), LV end-systolic diameter (LVESD), intraventricular septal (IVS) and posterior wall (PW) were measured in parasternal view. In sum, relative wall thickness (RWT) = (IVS + PW) / LVEDD. Whereas in apical four-chamber view the right ventricular internal diameter (RVID), tricuspid annular plane systolic excursion (TAPSE) by M-MODE technique, and LV volumes were measured. LVEF was calculated using the biplane Simpson's method. The mitral diastolic velocity (E and A velocities, E deceleration time – DT), Em (the average from septal and lateral by tissue Doppler), and E/Em ratio were calculated. Tissue doppler was used for measurement the maximum systolic annular velocity (S') for RV (S'RV).

Speckle tracking parameters

Two-D longitudinal *speckle tracking* analysis was performed with the use of three endocardial markers (at the end-diastolic frame: at apical four- and three-chamber views). EchoPAC software automatically tracked the contour of endocardium and later this was verified (and corrected if necessary) as described in literature [15]. To quantify the apical and basal LV rotations, appropriate short-axis planes were scanned [16]. Counter-clockwise rotations (from the LV apex) was calculated as a positive; whereas clockwise rotations - a negative value. LV twist was the highest net difference in degrees between the apical and basal rotation. LV torsion was defined as LV twist indexed by LV diastolic longitudinal length. Peak systolic (peak rotation) velocity and early diastolic apical and basal rotation (untwisting) velocity were derived from rotation rate curves.

LA strain 2D

Two- and four-chamber apical views were determined by finding the largest long-axis. Due to the absence of an LA-specific software, we used software dedicated to LV analysis as described in the literature [15, 17].

3D parameters

The appropriate software (4DQ analyses) was used for LV end-systolic, end-diastolic volumes, LVEF and 3D strains measurement. Calculation of 3D area strain (3D-AS) which means global longitudinal plus circumferential strain, and 3D global radial strain (3D-RS) was performed by averaging the end-systolic segmental values when at least 14 segments had acceptable tracking [16, 18].

We divided all patients in 2 groups according their age: below 60 years of age (<60) and 60 years or older (≥60). The further analysis were compared between these subgroups. The protocol of the study was accepted by the Local Ethics Committee and written informed consent was obtained from all participants.

Statistical analysis

All continuous data were presented as median (25th-75th), categorical data in proportion. Mann-Whitney U test and Pearson's chi-square test were used to compare the differences between the groups. P value <0.05 was considered statistically significant. The statistical analysis was performed using the R 2.15.2 environment.

Results

From enrolled 53 patients, subgroups <60 yo and ≥ 60 yo was formed of 39 and 14 patients respectively. The higher incidence of hypertension, type 2 diabetes and hyperlipidemia was observed in the older group, differences in frequency of ischemic heart disease reached statistically significant values (Table 1). Particularly noteworthy is the frequency of atrial fibrillation, which was similar in both subgroups, older and younger. However, the 5-year risk of sudden cardiac death, calculated using the European Society of Cardiology calculator was lower in older people [2]. This result was of borderline statistical significance.

Analysis of the standard echocardiohraphic parameters showed a worse diastolic function in the older

Table 1. Clinical characteristics of < 60 and ≥ 60 HCM patients

	HCM < 60 n = 39	HCM ≥ 60 n = 14	P
5-year risk of SCD	**4.0 (2.9 - 7.4)**	**3.6 (2.2 - 3.9)**	**0.077**
Arterial Hypertension	18 (45%)	13 (65%)	0.177
Coronary Artery Disease	**0 (0%)**	**3 (15%)**	**<0.033**
Diabetes Melitius type 2	5 (12.5%)	5 (25%)	0.278
Hyperlipidaemia	22 (55%)	15 (79%)	0.091
Atrial Fibrillation / Atrial Flutter	11 (27.5%)	6 (30%)	1.000
Family history of Sudden Cardiac Death	8 (20%)	5 (25%)	0.744
Cardiac Arrest	3 (7.5%)	2 (10%)	1.000
Non-sustained Ventricular Tachycardia	11 (27.5%)	5 (26%)	1.000
Intravenous Cardioverter-Defibrillator	11 (27.5%)	4 (20%)	0.753

HCM – Hypertrophic cardiomyopathy; SCD – Sudden Cardiac Death

Table 2. Standard echocardiographic parameters in < 60 and ≥ 60 HCM patients

	HCM < 60 n = 39	HCM ≥ 60 n = 14	P
HR (bpm)	64 (60-70)	60 (54-64)	<0.0310
AVC (msec)	360 (329-401.7)	365.5 (343-421.7)	0.1839
LADs (mm)	45 (43 - 48)	44 (42-46)	0.107
LAA index	14.1 (12.9-16.0)	15.0 (12.3-16.0)	0.439
LAV index (ml/BSA)	56.7 (42.7-62.7)	50.7 (38.9–57.4)	0.113
LV mass index (g/BSA)	117 (110-136)	115 (111-117)	0.309
LVEDd (mm)	40 (36-44)	41 (36-42)	0.469
LVESd (mm)	23 (21-25)	24 (19-26)	0.485
E/A	**1.2 (0.8-1.5)**	**0.8 (0.7-0.9)**	**<0.028**
DecT (msec)	**173 (147-232)**	**267 (201-315)**	**<0.001**
A dur mitr (msec)	157 (143-179)	173 (156-194)	0.076
Em (cm/s)	**0.06 (0.05-0.08)**	**0.05 (0.05-0.07)**	**<0.029**
E/Em	**10.2 (7.9-13.9)**	**12.0 (10.2-17.7)**	**<0.033**
S pulm (m/s)	0.56 (0.48-0.64)	0.65 (0.51-0.78)	0.089
D pulm. (m/s)	0.45 (0.36-0.52)	0.40 (0.33-0.50)	0.356
A pulm (m/s)	**0.31 (0.27-0.37)**	**0.37 (0.32 0.43)**	**<0.026**
A dur pulm (msec)	**111 (97-125)**	**134 (125-155)**	**<0.012**
LVEDV (ml)	**99 (82-114)**	**65 (49-84)**	**<0.025**
LVESV (ml)	**35 (26-445)**	**18 (14-26)**	**<0.006**
LVEF (%)	65 (59-69)	64 (52-71)	0.319

HCM – Hypertrophic cardiomyopathy, BSA – Body surface index; HR – heart rate, AVC – aortic valve closure, LADs - left atrial diameter, LAA index - Left atrial area index, LAV index – Indexed Left atrial volume, LV mass index – Indexed Left Ventricular mass , LVEDd - left ventricular end-diastolic diameter, LVESd - Left ventricular end – systolic diameter, E/A – the ratio of early-to-late peak mitral velocities, DecT - Deceleration time, A dur mitr. – Mitral Adur, Em – early diastolic mitral myocardial peak velocity averaged from two positions, E/Em – ratio between E and Em, S - pulmonary venous systolic wave, D - pulmonary venous early diastolic wave, Adur pulm – Pulmonary Adur, LVEDV - Left ventricular end-diastolic volume, LVESV- left ventricular end-systolic volume, LVEF - Ejection fraction

Table 3. 2D- and 3D – strain parameters in < 60 and ≥ 60 HCM patients

	HCM < 60 n= 39	HCM ≥ 60 n= 14	P
2D LA peak strain 4Ch (%)	15.0 (12.3-19.6)	18.3 (14.1-19.0)	0.265
2D LA peak strain 2Ch (%)	18.6 (13.1-23.9)	19.0 (17.2-22.5)	0.467
2D - Br (°)	-8.4 (-11.9/-5.4)	-7.4 (-10.5/-4.9)	0.292
2D - Ar (°)	12.0 (8.1-16.6)	16.1 (9.8-17.1)	0.310
2D - Twist (°)	21.01 (16.0-25.0)	21.1 (16.0-25.0)	0.298
2D - Torsion (°/cm)	2.9 (2.2-3.3)	2.0 (1.8-3.5)	0.447
2D - Peak LV twisting rate (°/sek)	110.5 (81.5-133.5)	112.7 (91.9-123.0)	0.462
2D - Peak LV untwisting rate (°/sek)	-101.7 (-135.7/-61.5)	-84.2(-113.6/-72.2)	0.280
2D – GLS (%)	-14.8 (-17.0/-12.7)	-16.0 (-19.8/-12.3)	0.196
3D – AS (%)	**-22.0 (-25.8/-19.3)**	**-26.0 (-25.8/-19.3)**	**<0.037**
3D - RS (%)	**33.0 (27.3-40.0)**	**40.0 (34.0-46.0)**	**<0.031**

GLS – global longitudinal strain, Br –maximal basal rotation, Ar – maximal apical rotation, Twist – twist of the left ventricle, Torsion – torsion of the left ventricle, RS – radial strain, AS – area strain

subgroup (values of E/A, decT, Em, E/Em, A pulm and A dur pulm parameters - see Table 2). The 2D-peak LV untwisting rate parameter which corresponds to the diastolic function was worse in the older group, although the differences were not reach statistical significance (Table 3). In ≥60 HCM patients we found significantly lower LV volumes (Table 2).

The 2D speckle tracking analysis did not reveal statistically significant differences between the subgroups, although it should be noticed, that the longitudinal strain, measured by 2D-GLS, was worse in the subgroup <60. The 3D strain parameters were significantly worse in younger HCM patients.

Discussion

Our findings revealed a number of clinical and echocardiographic differences among patients with HCM. As expected, our older patients (≥60) had more comorbidities (particularly coronary artery disease), which was in accordance with the data from the literature and consistent with population data [20]. The incidence of atrial fibrillation (AF) among the study population deserves the special attention (Table 1). In the general population the frequency of AF increases with age [21], whereas in our study every 3rd-4th patient in both age groups had history of AF. This arrhy-

thmia is the most common complication of HCM, thus rigorous monitoring for its occurrence is necessary and the anticoagulant treatment should be administrated regardless the CHA2DS2-VASc score [2, 21].

The early appearance of diastolic dysfunction in HCM patients is a common symptom described in the literature [19, 22]. In the healthy population diastolic dysfunction progresses with age and is a proof of the natural aging process in the myocardium [23]. As a matter of fact, in our study the diastolic dysfunction was more expressed in patients ≥60, but also in younger patients those parameters were worse than in a healthy population of corresponding age [19, 22-23]. It is known that the parameters of size and function of LA deteriorate with the progression of diastolic dysfunction. It is also known that the processes of fibrosis and hypertrophy of LV always goes straightforwardly with remodelling of LA [24]. This statement has a proven predictive value; for example Iioi et al demonstrated that serious cardiac events in HCM patients were independently related with increased LAVI [4]. The results of our study confirm that dependencies: our patients in both age groups had increased LADs, LAAI and LAVI in comparison to the healthy population from the literature [4].

An important parameter evaluated in our study is LA speckle tracking analysis. The data from literature indicate the potential usefulness of the speckle tracking technique in predicting the cardiac events among HCM patients. For example Fujimoto et al proved that LA peak longitudinal strain <20.3% is associated with an increased risk of heart failure and atrial fibrillation in the follow up [17, 25]. A similar observation was also presented by the other authors [4, 10, 15]. In our study, in both age subgroups the LA peak longitudinal strain was <20.3% (Table 2), which may have significant clinical implications and requires further research.

LVEF in persons with HCM is usually preserved or increased when compared with the healthy population [26]. Our study confirms that the median value of LVEF in both age subgroups was >50% (the lower limit of normal range) (Table 2). However, LV longitudinal strain is usually worse in HCM patients than in healthy people which is in agreement with our results. The median value of 2D-GLS for an older and younger subgroups stood at -16.0% and -14.8% respectively, whilst in healthy population the value of 2D-GLS stands at -20% and more [27]. Debonnaire et al present interesting analyses, which show that the values of 2D-GLS <14% and LAVI >34ml/m2 are independent predictors of adequate therapy of cardiac implantable cardioverter-defibrillators [3, 6]. In turn, Verge et al specifies the strain of the myocardial areas affected by hypertrophy as a predictor of sudden cardiac death [6].

Currently we can observe rising interest in myocardial strain analysis with the use of 3D echocardiography [18]. Our study presents interesting results in that regard: the area strain parameters (obtained by addition of longitudinal and circumferential strains), as well as the radial strain, were statistically significantly worse in the subgroup <60 yo (Table 3), which is in agreement with the literature and directly indicates on worse systolic function in younger subgroup [18].

Other interesting parameters, measured by the speckle tracking technique, are LV twist and torsion, which according to Zhang et al may be used as an echocardiographic marker of fibrosis grade in HCM patients [5, 7]. The above-mentioned study shows that the LV twist and torsion are much higher in patients with myocardial fibrosis confirmed by the cardiac magnetic resonance examination. The authors also suggest that thanks to these parameters, the speckle tracking echocardiography may be useful for assessing the grade of myocardial fibrosis [7]. In our study there were no differences between the age subgroups in terms of the extent of LV twist and torsion, although this topic undoubtedly requires further research.

Our study has a low sample size, which is partially the result of a highly selective enrollment process to achieve the best quality of images (FR from 50 to 80 frames/sec). Thus, larger study groups are strongly needed to verify our results. Secondly, our results were not verified by another imaging technique, for example cardiac magnetic resonance.

Conclusions

Older HCM patients are characterized by a higher incidence of coronary artery disease, while younger ones by atrial fibrillation, which occurs far more often than in the general population. An echocardiographic analysis indicates worse diastolic function in group ≥ 60 yo and worse systolic function (measured by speckle tracking technique) in group < 60 yo. The clinical relevance of analysed echocardiographic parameters, especially in terms of prognosis of the HCM patients, requires further research with a larger sample size.

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EUROPEAN JOURNAL OF TRANSLATIONAL
AND CLINICAL MEDICINE 2019;2(1):36-43

RESEARCH ARTICLE

Sources of medical information of patients referred to colorectal surgery outpatient clinic for hemorrhoidal disease

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Abstract

Background: We surveyed patients with hemorrhoids about their behavior regarding searching for information about that disease and confronted it with data obtained from Google Trends website and Google searches. We aimed to determine sources of information on hemorrhoids used by patients. Secondary aim was to assess the quality of information provided by Internet in particular. **Materials and methods:** We collected 78 surveys from patients of the outpatient surgical clinic at Medical University of Gdańsk, in which we asked about sources of information about hemorrhoids. We used Google Trends to analyze most often used search queries associated with that topic. In result, we analyzed the content of top 10 Google search results of that queries in order to verify reliability. **Results:** Over 80% of surveyed patients looked for information about that disease online, 50% of whom were satisfied with the quality of information obtained. Our Google Trends analysis showed that term hemorrhoids has overwhelming prevalence in comparison to remaining terms. Analysis of top 10 Google search results showed that 7 in 10 organic links lead to websites with professional information about hemorrhoids. **Conclusions:** Patients use the Internet as a source of knowledge about hemorrhoids and find it satisfactory. Moreover, our research indicates that this information is reliable.

Keywords: hemorrhoids • Internet/Patient Preference • Google Trends • search engine

Citation

Spychalski P, Perdyan A, Łaski D, Kobiela J, Błażyńska-Spychalska A, Łachiński A, et al. Sources of medical information of patients referred to colorectal surgery outpatient clinic for hemorrhoidal disease. Eur J Transl Clin Med. 2019;2(1):36-43.
DOI: 10.31373/ejtcm/105778

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No external funds.

Available online: www.ejtcm.gumed.edu.pl

Introduction

Nowadays, patients' self-consciousness is rising with World Wide Web as one of the most important sources of medical knowledge [1]. It is caused both by the growing amount of medical content in the Internet and by the growing percentage of population with Internet access [2-3]. Besides medical literature, newspapers and pamphlets, patients often choose the Internet which seems to be more accessible source of information about bothersome symptoms than a visit in physician's office. While self-diagnosing techniques (e.g. self palpation of the perianal area or self examination per rectum) which are explained on the Internet may seem sufficient in some cases, hemorrhoids should be diagnosed by a medical practitioner. Hemorrhoidal disease should be diagnosed after detailed history-taking and an accurate physical examination, including *per rectum* examination [4]. Moreover, internal hemorrhoids, which do not prolapse, can only by diagnosed by physician [5].

In this study we aim to determine sources of information on hemorrhoids used by patients. Secondary aim of the study is to assess the quality of information provided by Internet in particular.

Materials and methods

Study concept

We hypothesized that patients often search for information about hemorrhoidal disease independently and that Internet may be an important source of this information. Therefore, we designed this study in three-stage manner. As a first step we collected from patients surveys on hemorrhoidal disease. As a second step, based on the information gathered from surveys, we conducted a Google Trends analysis. In the final step we analyzed information on the patients' search behavior and assessed the quality of information they found in the Internet.

Survey

We collected 78 surveys from 78 patients of the outpatient surgical clinic at the Medical University of Gdańsk. The survey was anonymous and voluntary. Only the patients referred from general practitioner with either a suspicion or diagnosis of hemorrhoids were asked to complete the survey. Survey established following information: respondents' demographics, availability of an Internet connection, cause of the visit, presence or suspicion of hemorrhoids, source of knowledge about symptoms and treatment, reliability of that information and information about self-medication. Statistical calculations were made with Statistica 12 software (2014, Stat Soft, Inc., Tulsa, USA).

Google Trends

On 14.09.2018 we queried Google Trends and downloaded the data for the following search input ["hemorrhoids"+"anal varices"+"anal bleeding"] [original polish queries: "hemoroidy"+"żylaki odbytu"+"krawawienie z odbytu"] Based on methodology suggested by Nuti et al [6]. Although hemorrhoids and anal varices are synonymous but rather two different diagnoses, we chose to include them in the search query as in common language they are often used interchangeably by mistake [7]. We searched within Poland from January 1st 2006 to September 1st 2018. All query categories were used. We narrowed regional interest to Poland, because of language specificity of the query.

Upon initial Google Trends search we narrowed the queried terms to "hemorrhoids" because it was the most often used term according to Google Trends in comparison to remaining terms (79 vs 6 vs 6 respectively).

Results in Google Trends are shown in a relative manner. Numerical data values represent search interest relative to the highest point on the chart for the given region and time. A value of 100 is the peak popularity for the term. Popularity is measured in comparison to all of Google searches in specified time and location. A value of 50 means that the term is half as popular. Likewise, a score of 0 means the term was <1% as popular as the peak results [8].

Internet reliability

Based on the previously determined search term we conducted a Google search and analyzed results from the first page and screened professional or non-professional websites. Each link was categorized into: organic (if it was an organic Google search result) or advertisement (if it was part of the Google Ad Words campaign); professional (if it was authored by a Medical Doctor (MD) or based on medical literature) or non-professional (drug company website, health-promoting website, outpatient clinic website or an open encyclopedia).

The first page of search results represents over 90% of the traffic and thus second and further pages weren't included into the study [9]. We chose not to assess data from either MSN or Yahoo! due to Google's overwhelming market-share in Poland [10]. On 21.08.2018 and 28.08.2018 two researchers with medical background performed 2 separate series of searches for the term "hemorrhoids" using Google

Chrome, Firefox, Opera, Google Chrome Mobile, Safari Mobile web browsers. All searches were done in "incognito mode" to exclude any interference from cached files. Four most popular Google Ad Words results were chosen to be included into the study.

Results

Survey

Abbreviated results are presented in Table 1. Full results are available in Appendix 1. Median age of participants was 47 years. Definite majority of respondents were female, university-educated and living in urban areas. Almost 9 out of 10 patients had Internet access. Most common causes for referral to the colorectal surgery outpatient clinic were: suspicion of hemorrhoids (53.8%) and diagnosed hemorrhoids (28.2%). Most patients (73.1%) diagnosed themselves, while physician diagnosing remaining 26.9% was either GP or a specialist. Less than 1 in 4 patients were ever examined per rectum.

Majority of patients (80.8%) undertook Internet search regarding hemorrhoidal disease and half of them were satisfied with the results. Among most common sources of knowledge on the diseases and their treatment (% respectively) were: physicians (44.9%; 53.8%) and the Internet (44.9%; 32.1%). Over half of the respondents self-medicated, most often with suppositories (46.2%) and creams or ointments (44.9%). Almost 1/3 changed their diet. In over 7 of 10 of cases those efforts were at least partially successful.

Personal computer was the most common device used to access the Internet (74.4%) while mobile devices placed second (27%). Scientific associations' WebPages, scientific journals' WebPages and National Health Fund (NFZ) webpage were generally found to be trustworthy while Internet forums, popular media, pharmaceutical companies' WebPages and WebPages for patients were not. Only 1 in 5 respondents chose to attach suggestions regarding improvement of the available information. The most frequently mentioned ideas were: the physician should collect a more detailed patient history (25%), pamphlets in outpatient clinics (19%), creating a dedicated medical web service (19%) and easier access to specialists (41%).

Table 1. Abbreviated results of the survey

Did you look for information about hemorrhoids?	n = 78	%
Yes	63	80.8%
No	13	16.6%
Not answered	2	2.6%
Were you satisfied with the information you obtained?	n = 78	%
Yes	40	51.3%
No	30	38.4%
Not answered	8	10.3%

What was your source of information about symptoms of hemorrhoid disease? (multiple choice question)	n = 78	%
Physician	35	44.9%
Newspapers	30	38.5%
Pamphlets	25	32.1%
Internet	35	44.9%
How many sources of information about symptoms did you use?	n = 78	%
One	23	29.5%
More than one	55	70.5%

Appendix for table 1. Abbreviated results of the survey

Was this information helpful?		
	n = 78	%
Yes	67	85.9%
No	6	7.7%
Not answered	5	6.4%
Have you tried self-treatment?		
	n = 78	%
Yes	42	53.9%
No	27	34.6%
Not answered	9	11.5%
Was the treatment successful?		
	n = 78	%
Yes	22	28.2%
Partially	34	43.6%
No	9	11.5%
Not answered	13	16.7%
What type of treatment have you used? (multiple choice question)		
	n = 78	%
Diet	25	32.1%
Hygiene	16	20.5%
Ointments and creams	35	44.9%
Suppositories	36	46.2%
Tablets	10	12.8%
How many types of treatment did you use?		
	n = 78	%
One	30	38.5%
More than one	35	44.9%
Not answered	13	16.6%

Do you have access to the Internet?		
	n = 78	%
At home, tablet, smartphone	68	87.1%
At friend's or family's home	0	0.0%
Other	2	2.6%
No	7	9.0%
Not answered	1	1.3%
What is the cause for your visit?		
	n = 78	%
Suspicion of hemorrhoids	42	53.8%
Confirmed hemorrhoids	22	28.2%
Else	10	12.8%
Not answered	4	5.2%
Did your GP performed a per rectum examination?		
	n = 78	%
Yes 26.3% (n=19)	5	6.4%
No 73.7% (n=19)	14	18%
Not answered	59	75.6%
Did you look for information about hemorrhoids?		
	n = 78	%
Yes	63	80.8%
No	13	16.6%
Not answered	2	2.6%

Appendix for table 1. Abbreviated results of the survey

What kind of device did you use to access information about symptoms of hemorrhoid disease? (multiple choice question)	n = 78	%
Personal computer	58	74.4%
Tablet	8	10.3%
Smartphone	13	16.7%
TV	9	11.5%

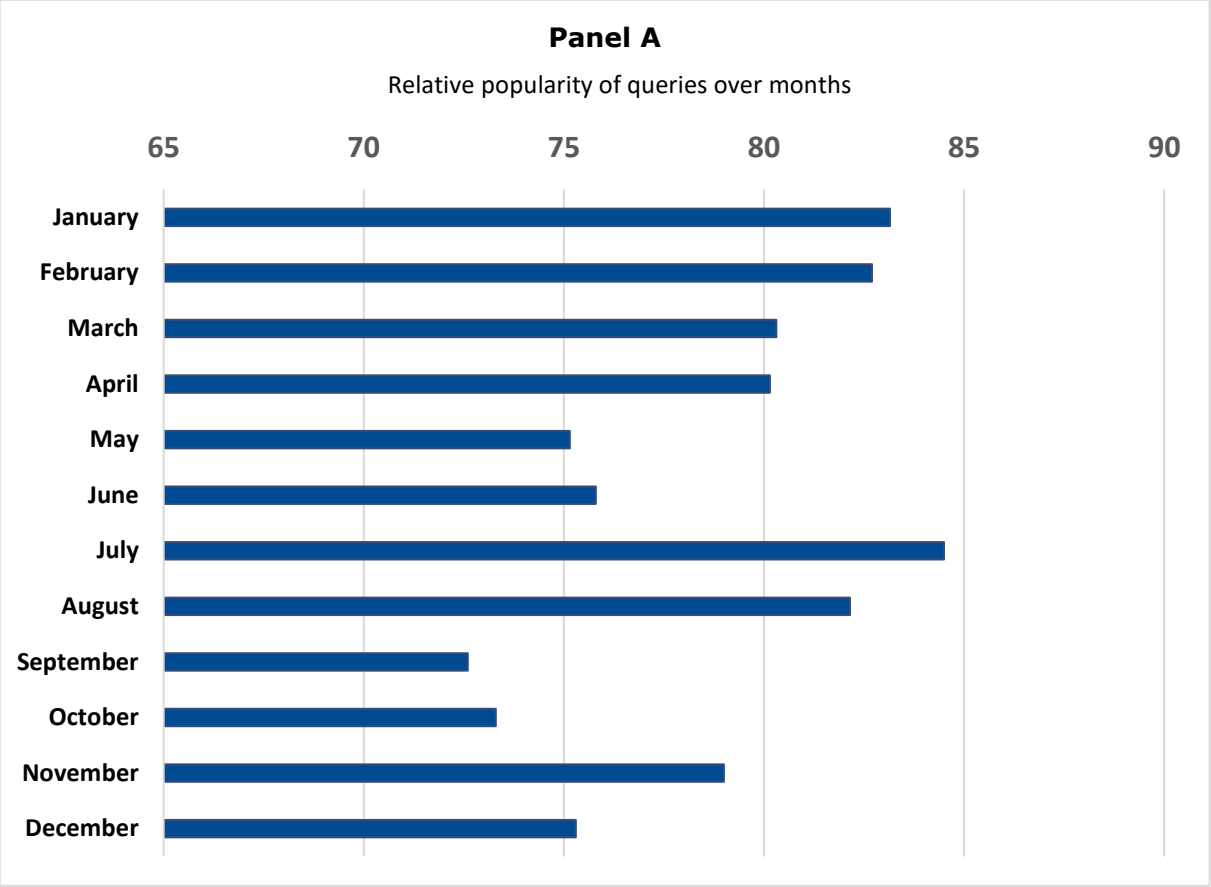
Google trends

Changes in the amount of search queries over last 12 years were observed with median at 82 and minimal interest at 54 (maximal at 100 - as a result of calculation method). However there is a visible yearly pattern with lowest interest before and after holidays and during Christmas (respectively in May, June, September, October and December (75.2; 75.8; 72.6; 73.3; 75.3)) and highest during holidays and after Christmas (respectively January, February, July and August (83.2; 82.7; 83,4; 82.4)). (Graph 1, Panel B)

Variation in the amount of search queries across geographical location was observed with the lowest interest in Lodzkie and Zachodniopomorskie (87) voivodships and highest in Opolskie, Podlaskie, Swietokrzyskie and Lubuskie voivodships (100).

Internet reliability

First page of Google results for search term “hemorrhoids” was analyzed. Each contained 10 organic links and varying amount (from 1 to 4) of Ad Words



Graph 1: Panel A. Relative popularity of queries over the months of the year 2006-2018

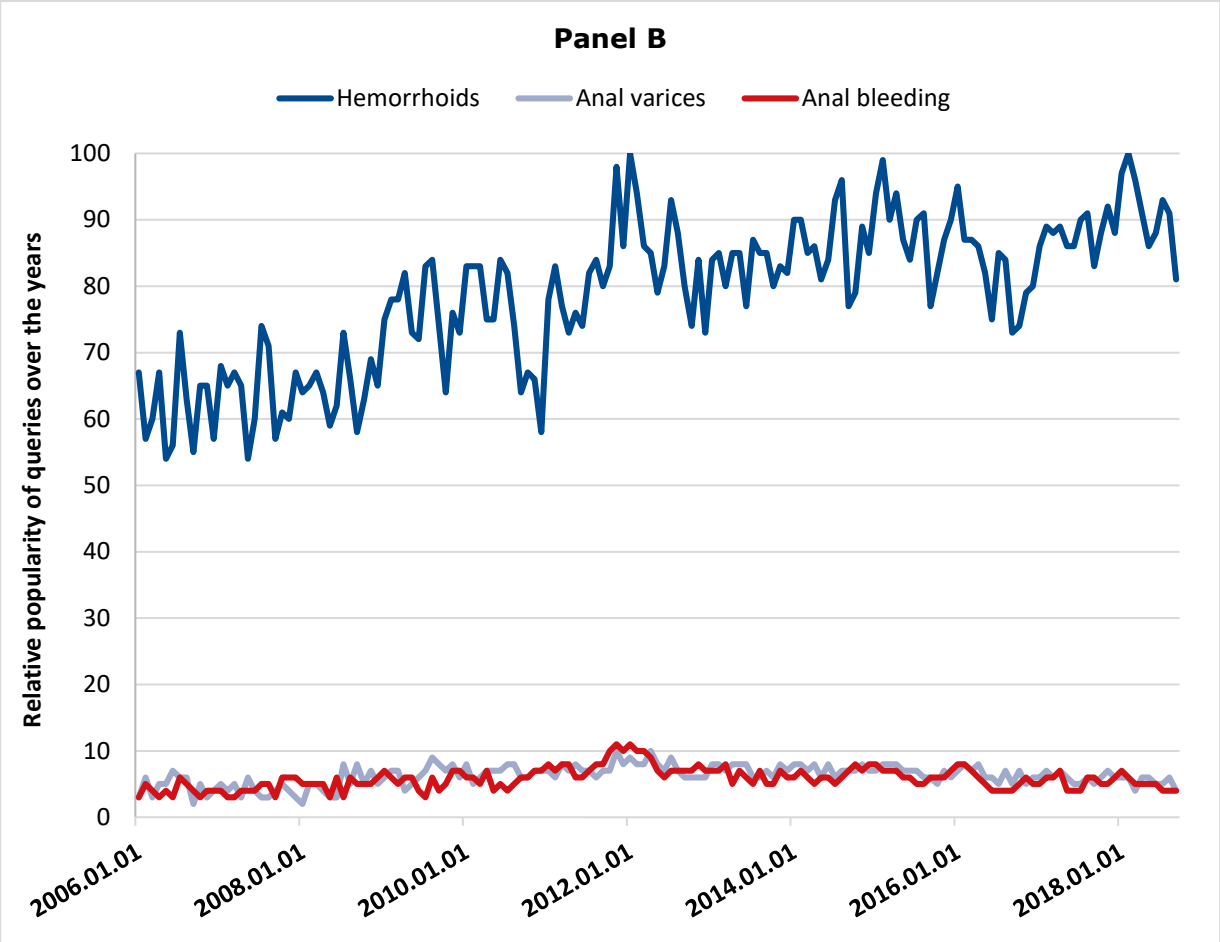
advertisement links [11]. Ad Words is a Google Inc. advertisement campaign tool which allows vendors to advertise their products and services in text-based search ads. Content of the displayed ads depends on searched terms, cached files and other factors [12]. Below we present results from analysis of links provided by the first page of Google search results. One hundred and twenty-one links were analyzed of which 21 were advertisements and 100 were organic. Only those ads that were displayed in at least 2 separate searches were included.

Total of 21 Ad Words ads linked to 4 websites of which 3 were non-professional and provided by drug companies, whereas 1 was categorized as professional (provided by a private practice outpatient clinic and authored by a MD).

Every analyzed Google search page contained the same 10 organic links of which 3 were non-professional and 7 were professional. Two out of three of the non-professional websites were provided by drug companies and presented modes of treatment and remaining one was a health-promoting website however it lacked literature sources or authorship information. Of the 7 websites classified as professional, 1 was an encyclopedia (therefore based on medical literature) and the remaining 6 were health-promotion websites (1 based on literature, the rest were authored by MD). Results with links to analyzed websites are in Table 2.

Discussion

Over 80% of the patients referred to our surgical outpatient clinic previously looked for information about hemorrhoids, thus showing a great demand for knowledge among them. Moreover, 73% of patients stated that they performed a self-diagnosis of hemorrhoids. In our group, Internet was used as often as professional advice to research the topic of hemorrhoids and overall percentage of patients that used Internet was 45% and similar to the findings of Diaz et al [13]. In contrast, over 87% (1016/1162) of the patients analyzed by Wong et al used the Internet to find health information. The most common sought topic was symptom 81.59% (829/1016) and the most common reason for choosing Internet was convenience 55.41% (563/1016) [14].



Graph 1: Panel B. Relative popularity of queries over the years (cumulated data from years 2006-2018)

Table 2. Complete results of the internet reliability analysis

Lp	Links in order of search results	Category	Authorship	Organic/Ad	Type of website
1	http://jmalys.pl/hemoroidy.html	Professional	MD	ad	outpatient clinic
2	http://www.criorectum.pl	Non-professional	lack of data	ad	drug company
3	http://procto-hemolan.pl	Non-professional	lack of data	ad	drug company
4	http://www.fine6.pl	Non-professional	lack of data	ad	drug company
5	http://www.poradnikzdrowie.pl	Professional	MD	organic	health website
6	http://www.poradnikzdrowie.pl	Professional	MD	organic	health website
7	http://www.medonet.pl	Non-professional	lack of data	organic	health website
8	http://wylecz.to	Professional	MD	organic	health website
9	http://proctohemolan.pl	Non-professional	lack of data	organic	drug company
10	https://pl.wikipedia.org	Professional	based on literature	organic	encyclopedia
11	http://www.criorectum.pl	Non-professional	lack of data	organic	drug company
12	https://portal.abczdrowie.pl	Professional	based on literature	organic	health website
13	http://gastrologia.mp.pl	Professional	MD	organic	health website
14	http://lubikowski.pl	Professional	MD	organic	health website

Medical professionals often have to struggle against their patients' misinformation. While it is a common belief that information that can be found on the Web is of low quality, our research shows that it is not necessarily true. Majority of the analyzed websites are authored by MDs or are based on medical literature, and are easy to understand. That may explain why as many as 63% of patients that researched hemorrhoids were satisfied with the information they obtained. On the other hand, quality of the information on the Web concerning different colon diseases is not always satifactory. Yeung et al showed that out of 200 websites about surgery for diverticular disease only 60 (30%) provided patient-oriented information. Despite the fact that, symptoms, complications, investigations and treatment options were thoroughly described, only 22 (36.7%) of the websites were found as information relevant [15]. In addition, analyzing 100

sites about surgical treatment for Crohn's disease only half of them provided details on treatment options and only one was recognized as informative [16].

Our study has some potential limitations. We observed a much higher percentage of women in our patient group what is not explained by published epidemiology of hemorrhoidal disease this however may be a random occurrence [17]. Moreover, our data may be biased due to the fact that surveys were collected in a specialized surgical outpatient clinic. Localization of our clinic in a large city may have influenced the demographics of our study group. The mechanisms of Google search engine may be another limitation. While organic links are presented in the same order for every user due to SEO (Search Engine Optimization), Ad Words are specific for every internet user's location, search patterns and cached files. That is why every search is unique to the user and cannot be fully reproduced. In addition, we expect that some of our participants may have used advertisement blocking tools which prevent many ads from appearing on their screens, thus making the searches completely different.

Conclusions

We would like to underline the fact that Internet is a source of medical information which patients prefer and consider as important. Additionally, the knowledge available on the Internet is freely accessible and of good quality. Both doctors and public campaigns should consider patients' preferences in obtaining medical knowledge and point them to quality sources.

Acknowledgements

The study is no financial support for the described research. The authors do not have any conflicts of interest to declare.

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EUROPEAN JOURNAL OF TRANSLATIONAL
AND CLINICAL MEDICINE 2019;2(1):44-47

RESEARCH ARTICLE

Postponed absorption of dabigatran in a patient with paralytic ileus – difficulties in decision making on reversal agent (idarucizumab) use

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Abstract

According to the European Society of Cardiology (ESC) guidelines, non-vitamin K antagonist oral anticoagulants (NOACs) are first choice drugs in prevention of thromboembolic events among patients with atrial fibrillation (AF). According to our knowledge this was the only case of delayed absorption of dabigatran due to ileus. A 79-year-old woman with hypertension and a 1-year history of persistent AF treated with dabigatran (a direct thrombin inhibitor approved for the prevention of stroke in patients with non-valvular AF) 110 mg bid for two weeks. She was hospitalized due to acute abdominal pain, vomiting and diarrhea. Signs of acute embolism of abdominal aorta (paraparesis) were confirmed on contrast-enhanced computed tomography scan and she was qualified for emergency surgery. The use of idarucizumab, the specific reversal agent for dabigatran, was considered twice. This case shows that exposure to dabigatran may occur later in patient with acute ileus due to alterations in absorption than it can be expected in normal situation. Such patients should be carefully monitored for a significant rebound in anticoagulant activity.

Keywords: idarucizumab • dabigatran • paralytic ileus • absorption

Citation

Tomaszuk-Kazberuk A, Łopatowska P, Młodawska E, Klaja B, Ausztol P, Korbel B, Sobkowicz B. Postponed absorption of dabigatran in a patient with paralytic ileus – difficulties in decision making on reversal agent (idarucizumab) use. Eur J Transl Clin Med. 2019;2(1):44-47.
DOI: 10.31373/ejtcm/109298

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Updated: 07.10.2019

No external funds.

Available online: www.ejtcm.gumed.edu.pl

Background

Idarucizumab, a dabigatran reversal agent, is the only antidote for NOACs available in Europe. In May 2018, andexanet alfa an antidote for factor Xa inhibitor (apixaban, rivaroxaban and edoxaban) was approved for sale in the United States of America. Idarucizumab is a humanized monoclonal antibody fragment that binds to dabigatran with a more than 350-fold higher affinity than dabigatran does to thrombin, therefore it instantly, specifically, strongly, and durably binds dabigatran and quickly reverses its anticoagulation effects [1]. The dabigatran–idarucizumab complex is biochemically stable and eliminated by the kidneys within a few hours. Dabigatran therapy may be reinitiated 24 hours after antidote administration. Efficacy and safety of idarucizumab was demonstrated in patients with major bleeding or who required urgent surgery or invasive procedures in the REVERSE-AD study [1]. Adverse reactions were observed in only ≤ 5% of patients and included headache and hypokalemia. Idarucizumab has been successfully administered in patients with life-threatening bleeding or before urgent major surgeries [2-4].

Aim

We wanted to analyze if exposure to dabigatran may occur later due to alterations in absorption in patients with acute ileus.

Results

Series analysis

A single occurrence of altered absorption of dabigatran triggered the documentation analysis of all patients treated with dabigatran due to AF since January 2017 to December 2018. In this single-centered retrospective study, 387 patients were reviewed for two endpoints: life-threatening bleeding and altered absorption of dabigatran. We recorded only two cases of life-threating bleeding in which idarucizumab was successfully used and one case of altered absorption of dabigatran.

Case description

A 79-year-old woman with hypertension and a 1-year history of persistent atrial fibrillation (AF) treated with dabigatran (Pradaxa®, Boehringer Ingelheim, a direct thrombin inhibitor that is approved for the prevention of stroke in patients with non-valvular AF) 110 mg bid for two weeks, was hospitalized due to acute abdominal pain, vomiting and diarrhea. Upon admission, the patient was dehydrated, with blood pressure of 165/65 mmHg and a heart rate of 85 beats/minute. The physical examination revealed abdominal tenderness and positive Blumberg's sign. The patient was given i.v. fluids, spasmolytics, painkillers and her condition markedly improved. Electrocardiogram (ECG) showed AF. Initial laboratory work-up revealed normal kidney function.

On the next day dabigatran was administered at 0800. Two hours later the patient presented with acute abdominal pain, paralytic ileus and deterioration of general condition. Signs of acute embolism of abdominal aorta (paraparesis) were confirmed on contrast-enhanced computed tomography scan and the patient was qualified for emergency surgery. Laboratory tests carried out 3 hours from dabigatran intake revealed activated partial thromboplastin time (APTT) of 29.7 sec (normal range: 24-35) and glomerular filtration rate of 66 mL/min. It was suspected that the patient did not swallow the tablet. The administration of idarucizumab (Praxbind®, Boehringer Ingelheim), the specific reversal agent for dabigatran, was considered before and during the surgery. Adequacy of intraoperative hemostasis was declared by the operating surgeon. Surprisingly, the post-operative lab results at 1500 were as follows: APTT 79.2 sec, thrombin time (TT) >240 sec (normal range: 14-21) and the dabigatran plasma concentration 207 ng/mL. The administration of the idarucizumab was considered once more. Finally the antidote was not administered because there were no complications during the operation, no signs of postoperative bleeding and the patient was in stable condition.

On the following day the patient was stable, conscious, with good verbal contact, dabigatran plasma concentration was 128 ng/mL, APTT 48.4 sec, TT 98 sec. Two days after operation the dabigatran plasma concentration was 46 ng/mL, APTT 48.5 sec, TT 69.1 sec. On the 5th postoperative day abdominal symptoms recurred. Computed tomography showed superior mesenteric artery embolism and embolectomy was successfully performed. After 20 days of hospitalization the patient was discharged to the Rehabilitation Department in stable condition. Clinical course of the patient is shown in Figure 1.

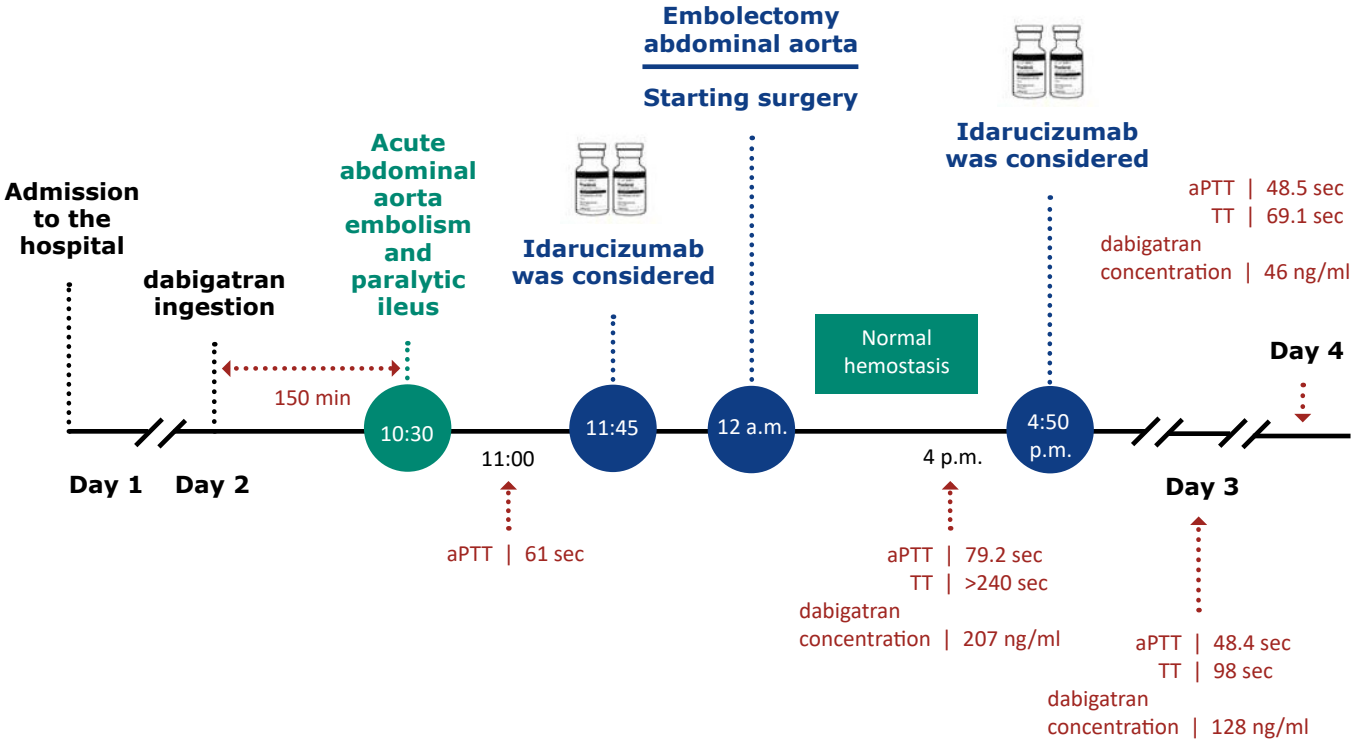

Figure 1. Clinical course of the patient. aPTT – activated partial thrombopladtin time, TT – thrombin time

Discussion

Shortly after starting treatment with dabigatran, a 79-year-old woman presented to the university hospital with abdominal discomfort. She was to be operated few hours after dabigatran ingestion. Surprisingly APTT was in middle of the normal range. In fact, during the initial part of the operation there was relatively efficacious coagulation according to the surgeon's assessment. The decision about idarucizumab administration was difficult but eventually reversal agent was not given.

Significant anticoagulant activity, however, reoccurred 5 hours after the operation, and a dabigatran plasma concentration of 207 ng/mL was measured 8 hours after the last ingestion of the drug. Idarucizumab was considered again, but based on the patient's improving condition and no signs of bleeding it was decided against reversal agent. The decision to withhold idarucizumab at that time point is a matter of debate. We are aware that some practicing clinicians would administer idarucizumab to avoid possible serious bleeding complications.

In our opinion this is a clinically important case. The dabigatran plasma concentration of 128 ng/mL obtained on day 2 is an interesting finding. In contrast, the literature describes median (10th–90th percentile) steady-state peak plasma concentrations of 133 (52–275) and 184 (74–383) ng/mL in patients with AF taking dabigatran at doses of 110 or 150 mg twice daily, respectively [5-6]. Thus, our patient had a therapeutic dabigatran plasma concentration about two half-lives after the last ingestion. The normal bioavailability of its prodrug (dabigatran etexilate) is 6–7% [7-8]. Thus, it is conceivable that the patient's paralytic ileus caused altered absorption, resulting in increased exposure to the anticoagulant a few hours later [8]. Our patient's coagulation markers such as APTT and TT corresponded with dabigatran plasma concentrations. We found one similar case in the literature; a patient with rectal perforation and peritonitis, who underwent emergency surgery complicated by severe bleeding stopped by idarucizumab and with postponed absorption of dabigatran [9].

Also according to the summary of product characteristics (SmPCs), dabigatran reaches maximum concentration in the plasma within 6 hours instead of 2 hours following administration in a postoperative period due to the influence of factors such as general anesthesia, gastrointestinal paresis, and surgical effects, regardless of the form in which it is orally administered [9-10]. Although these mechanisms remain not fully explained and at this time are speculative, alterations in absorption in conditions of ileus or acute peritonitis may potentially explain this phenomenon.

Dabigatran is considered as a safe drug according to both randomized trials and registries with low rate of major bleeding and a significant reduction of intracranial bleeding as compared to warfarin.

Conclusions

We conclude that exposure to dabigatran may occur later in patients with acute ileus than it can be expected in normal situation due to alterations in absorption. Such patients should be carefully monitored for a significant rebound in anticoagulant activity. The use of specific reversal agent for dabigatran in similar cases should be carefully and individually considered.

Funding

No funding has been received for preparation of this manuscript.

Conflict of interests

A. Tomaszuk-Kazberuk has received honoraria from Boehringer Ingelheim for lectures and consultations. B. Korbel is a medical manager in Boehringer Ingelheim.

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9. The summary of product characteristics (SmPCs): Pradaxa 150 mg.

EUROPEAN JOURNAL OF TRANSLATIONAL
AND CLINICAL MEDICINE 2019;2(1):48-52

SHORT COMMUNICATION

Usefulness of CartoMerge image integration module in catheter ablation of atrial fibrillation

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Abstract

Background: Anatomy assessment using Computer Tomography (CT) and Magnetic Resonance (MRI) is performed in patients undergoing pulmonary vein isolation (PVI). The aim of this analysis was to investigate whether electroanatomical 3D map and CT/MRI image integration using the CartoMerge system improves efficacy, reduces procedure time or fluoroscopy usage. **Materials and methods:** 57 patients undergoing PVI were divided in two groups: "Merge" (n=45 pts) and "non-Merge" (n=14 pts) depending on usage of image integration. PV isolation during procedure (acute PVI), procedure time, fluoroscopy time, number of radio frequency (RF) applications and AF recurrence during follow-up (Merge group: 12-24 months, non-Merge group: 9-18 months) were analyzed. **Results:** Intra-proceduaral PV was equal in both groups (93%). Long-term efficacy, defined as absence of AF recurrence, was insignificantly higher in the Merge group (69,8% vs 50%, p=0,11793). Procedure time was significantly longer in the Merge group – 239,1 (±55,5) min. vs 192,4 (±44,5). Fluoroscopy time was similar in both groups 29,9 (±12,23) vs 24,6 (±26,5) min, (p=0,579). Number of RF applications was significantly higher in the Merge group 48,5 (±25,2) vs 27,2 (±14,9). **Conclusions:** CartoMerge did not improve the rate of acute PVI, long-term effectivity or fluoroscopy time. In the non-Merge group the procedure time was shorter and the number of applications was significantly smaller.

Keywords: CartoMerge • Catheter ablation • atrial fibrillation • image integration

Citation

Drelich Ł, Królak T, Liżewska-Springer A, Kempa M, Kozłowski D, Raczak G, et al. Usefulness of CartoMerge image integration module in catheter ablation of atrial fibrillation. Eur J Transl Clin Med. 2019;2(1):48-52.
DOI: 10.31373/ejtcm/105891

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No external funds.

Available online: www.ejtcm.gumed.edu.pl

Introduction

Atrial fibrillation (AF) is the most common arrhythmia, with age-related incidence, reaching 5-15% in among people >80 years old. The increased and irregular heart rate of AF usually causes palpitations, and in more severe cases fainting, syncope or heart failure. Chaotic and uncoordinated electrical activity in the atria during AF reduces their mechanical function. Blood stasis, especially in left atrium appendage, leads to formation of thrombus, a potential embolic material which may cause cerebral stroke.

The pharmacological treatment of AF concentrates on 3 main goals: to reduce the frequency of AF episodes, to control of ventricular rate during arrhythmia and prevent thromboembolism. Limited efficacy of available drugs ant their numerous side-effects determined development of an alternative, invasive method – transcathether cardiac tissue ablation.

In 1997 Haisseguerre demonstrated the relationship between ectopic foci in pulmonary veins and AF [1]. High frequency impulses generated in those areas are the arrhythmia inducing ("trigger") and quite often sustaining factor ("driver"). Initially, ablation was targeted directly into those areas, but the coexistence of numerous foci and the risk of post-ablative vein stenosis led to the evolution of this procedure [1-5]. Nowadays, the most common method is pulmonary vein isolation (PVI) [6-9], with the objective of creating circular scars surrounding PVs (usually two scars, each surrounding a pair of left or right veins). Scars created during ablation are not able to conduct depolarization waves, thus in consequence the ectopic foci cannot influence LA tissue.

Pulmonary venous anatomy assessment is crucial for performing successful pulmonary vein isolation. Nowadays, electroanatomical systems are commonly used to create spatial maps of the LA and PVs. These tools provide more precise reflection of anatomical relations, increase precision of navigation and radio frequency (RF) application. Literature and clinical practice revealed high proportion of atypical pulmonary venous confluence variants. Imaging techniques like CT or nuclear magnetic resonance (NMR) allow determination of the number, size and the type of ostium of pulmonary vein [10-13]. Carto 3™ system (Biosense-Webster Inc.) used in our center is equipped in additional module – CartoMerge – allowing integration of 3D electroanatomical map with a 3D reconstruction of LA and PVs. The aim of this study was to investigate whether CartoMerge image integration module improves the PVI efficacy, reduces procedure time or fluoroscopy usage.

Materials and methods

The study population consisted of 57 patients undergoing PVI in the years 2012-2014. LA and PVs CT scan was routinely performed before the procedure. In the next step, the scans were imported to the Carto 3D system. Ablation strategy was the same in every patient. Ablation catheter and ring-shape Lasso diagnostic catheter were placed in LA via transseptal puncture, diagnostic electrodes were also placed in His bundle area (His) and in coronary sinus (CS) using transvenous access.

In the next step, electroanatomical 3D map were collected. In case of LA Point-by-Point or FAM technique was used – depending on operator's preference. After completing the mapping, in the first group of patients 3D map was integrated with the CT scan. Whereas in the second group the 3D CT scan was displayed as a separate picture in the 3D Carto system window. Choice was based on operator's preference.

After mapping, circumferential PV isolation was performed using an RF ablation catheter. Linear applications surrounding PVs in pairs were delivered – separately around pair of left and right veins. Ablation lines were located ~5-10 mm from the ostia of PVs in order to minimize the risk of post-ablation vein stenosis. Bidirectional conduction block in the ablation line was considered a criterium of electrical isolation. It was verified by pacing on one side of the line (LA and PVs) and signal analysis signals registered by the electrode on the opposite side. In some cases electrical cardioversion (ECV) under general anesthesia was necessary, resulting in prolonged procedure time.

Based on the procedure protocols and study registrations following data was analyzed: PV isolation during procedure (acute PVI), procedure time, fluoroscopy time, the number of RF applications. Moreover, the anatomy of PV ostia was analyzed using the 3D CT reconstructions and the radiologist's report. 4 veins with separate ostia were defined as typical. Different number of veins or common ostium was defined as atypical. None of the patients presented anomalous pulmonary venous drainage (PV ostium in heart chamber other than LA).

Follow-up visits were scheduled at 3, 6, 9, 12, and 24 months after the procedure. Medical history focusing on AF was collected, standard ECG and 24h Holter ECG were performed. In case of suspicion of AF recurrence, additional visits and investigations were administered.

Patients were divided into "Merge" and "non-Merge" groups depending on the usage of image integration. Follow-up lasted 12-24 months in the Merge group and 9-18 months in the non-Merge group.

Results

The merge group consisted of 43 patients (F=15) with average age of 53 (SD=13). Whereas the non-Merge group consisted of 14 patients (F=2) with average age of 51 (SD=11), p=0,63. The difference in AF type distribution was statistically not significant: 72% of Merge group patients suffered from paroxysomal AF and 57,1% in the non-Merge group (p=0,373). Typical PV anatomy was found in 72% (n=31) of patients in the Merge group and 78,8% in non-Merge group (p=0,8976). Detailed distribution is presented in table 1. Proportion of patients having ECV during PVI was similar in both groups (37,2% vs 35,7%).

PVI success rate was equal in both groups (93%). The long-term efficacy, defined as absence of AF recurrence, was higher than in the Merge group (69,8% vs 50%), but this difference was statistically insignificant. Procedure time was significantly longer the in Merge group: 239,1 (±55,5) minutes vs 192,4 (±44,5). Fluoroscopy time was similar in both groups 29,9 (±12,23) vs 24,6 (±26,5) min, (p=0,579). The number of RF applications was significantly higher in the Merge group: 48,5 (±25,2) vs 27,2 (±14,9).

Table 1. Distribution of clinical findings among the two study groups

	MERGE group n=43		non-MERGE group n=15		P value
Age	53	SD=13	51	SD=11	0,631302
Sex	F=15 M=28	F=34,9% M=65,1%	F=2 M=12	F=14,3% M=85,7%	0,259782
Paroxysomal AF	32	74,4%	8	57,1%	0,37298
Persistent AF	11	25,6%	6	42,9%	
Typical anatomy	31	72%	11	78,6%	0,897576
Atypical anatomy - RMPV	9	20,9%	0	0%	
Atpical anatomy – common left PV ostium	2	4,7%	3	21,4%	
Atpical anatomy – common left PV ostium + RMPV	1	2,3%	0	0%	
ECV during PVI	16	37,2%	5	35,7%	0,9197

AF – atrial fibrillation, ECV – external cardioversion, PV – pulmonary vein, RMPV - Right Medial Pulmonary Vein

Table 2. Characteristics and outcomes of the PVI procedure among the two study groups

	MERGE group n=43	non-MERGE group n=14	p
Acute PVI (%)	40 (93%)	13 (93%)	0,56112
Procedure time (SD) [min]	239,1 (±55,5)	192,4 (±44,5)	<0,008025
Fluoroscopy time (SD) [min]	29,9 (±12,23)	24,6 (±26,5)	0,05794
Number of RF applications (SD)	48,5 (±25,2)	27,2 (±14,9)	0,00036

PV – pulmonary vein, RF – radio frequency, SD – standard deviation

Discussion

The CartoMerge module was designed to improve PVI efficacy, reduce number of complications, reduce fluoroscopy time and whole procedure time. First articles describing CT/NMR integration with Carto 3D map during PVI were published in 2005-2007 [14-17].

Bartagella et al presented data from Carto Merge Italian Registry involving 12 centers [18]. Three different AF ablation strategies were analyzed: SOCA – segmental ostial pulmonary vein isolation (240 patients), CARTO – circumferential PV isolation using Carto 3D navigation (107 patients) and MERGE – CT/NMR scans integrated with 3D map using CartoMerge (226 patients). Total procedure time was significantly shorter in the MERGE group (210.3±63.4 vs. 231.7±70.7 min, $p < 0.04$), but longer than in the SOCA group (184.9± 58.4 min, $P < 0.0001$). Fluoroscopy time differences were insignificant (SOCA 56.5±22.5 vs. CARTO 55.0±25.3 vs. MERGE 54.3±25.5 min, $p = 0.98$). AF recurrence rate was lower in MERGE group (22.6%; $P < 0.0001$ compared to SOCA (44.6%) and CARTO (41.7%).

Kistler et al. Analyzed the impact of CartoMerge on PVI efficacy in a randomized trial comparing navigation using Carto electroanatomical mapping (EAM group, 40 pts.) and CartoMerge (CT group, 40 pts.) incorporating 3D reconstructions from CT scans [19]. There was no significant difference in PVI efficacy during 6 month follow-up (EAM - 56% vs CT – 50%) and long-term follow-up, including patients after Re-Do procedure Do (77% vs 71%). Fluoroscopy and procedure time did not differ significantly. In contrast to the Italian Registry, LA CT scan was performed in both groups and available to the operator, but data was imported to Carto system in CARTO group. Those conclusions suggest, that the radiological PV anatomy assessment is crucial for PVI efficacy, not image integration itself.

In our study in both analyzed groups CT scan was performed and imported to Carto 3D system, so use of image integration was the only difference between both groups. In the non-Merge groups CT reconstruction was displayed as separate picture in Carto 3D system, so data processing was exactly the same in both groups. That allowed us to strictly evaluate the influence of image integration on PVI efficacy.

In our study the long-term efficacy in Merge group was higher, but this difference was statistically insignificant, probably due to the small size of the non-Merge group. Moreover, in this group the incidence of persistent AF was higher (statistically not significant), and that is well-known factor correlating with lower efficacy of PVI.

Conclusions

Compared to LA visualization without integrating the image with Carto 3D map, the Carto Merge module did not improve the rate of acute PVI, long-term effectivity or fluoroscopy time. In the non-Merge group procedure time was shorter and the number of RF applications was significantly smaller.

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EUROPEAN JOURNAL OF TRANSLATIONAL
AND CLINICAL MEDICINE 2019;2(1):53-55

SHORT COMMUNICATION

The influence of the menstrual cycle on diameter and respiratory collapsibility of inferior vena cava in the population of young, healthy women – preliminary results

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Abstract

Introduction: Echocardiographic assessment of interior vena cava (IVC) is a part of estimation of right atrial pressure. In young women values exceeding norm are observed. The aim of our study was an echocardiographic assessment of IVC dimension depending on the phase of menstrual cycle among young, healthy women. **Materials and methods:** Female students of Medical University of Gdańsk were enrolled to the study. Each volunteer underwent echocardiographic examination of IVC diameter (d-IVC) and respiratory decrease in dimension in two time points, depending on the phase of menstrual cycle: in the first days of menstruation (Phase M), in the second part of menstrual cycle (Phase L). **Results:** 31 patients completed the study. There was a significant difference between the d-IVC in Phase M and Phase L (1.98±0.25cm vs 1.86±0.3cm; p <0.05). We did not observe correlation in terms of the inspiratory collapsibility. In the Phase M 77% patients achieved at least 50% decrease in dimension during inspiration comparing to 87% in Phase L (p=0.89). 35% patients had d-IVC exceeding reference values. **Conclusions:** In population of young women diameter of IVC exceeding reference values can be observed. IVC dimension dependents on the menstrual cycle.

Keywords: echocardiography • menstrual cycle • inferior vena cava

Citation

Nowak M, Dyda J, Barczyńska H, Ołubowicz M, Radtke A, Turek M, et al. The influence of the menstrual cycle on diameter and respiratory collapsibility of inferior vena cava in the population of young, healthy women – preliminary results. Eur J Transl Clin Med. 2019;2(1):53-55.
DOI: 10.31373/ejtcm/103002

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Introduction

Assessment of the inferior vena cava (IVC) from the subcostal window is part of a routine echocardiographic examination. Measurement of the IVC dimension and collapsibility during inspiration is used to noninvasively estimate right atrial pressure [1]. According to the 2010 American Society of Echocardiography guidelines, IVC diameter <2.1 cm and inspiratory collapse >50% correspond with normal right atrial pressure of 0-5 mm Hg [2]. Clinical practice shows that IVC values exceeding norms can be observed as an isolated abnormality in the population of young women.

The influence of female sex hormones on the cardiovascular system is well-acknowledged. Estrogen and progesterone affect cardiac performance and have an important role in atheroprotection. In addition, those hormones have direct impact on vessels through non-genomic mechanisms [3]. Female sex hormones have an effect on body fluid regulation, induce dilatation of the peripheral vessels and decrease venous flow. Furthermore, estrogen affects the synthesis of nitric oxide, while progesterone has diuretic activity. The concentration of female sex hormones depends on cyclic changes and present the lowest level of estrogene and progesterone during firsts days of menstrual cycle [4-5]. There is a lack of studies regarding the influence of those changes on IVC diameter measurement.

Therefore, the aim of our study was an echocardiographic assessment of IVC dimensions depending on the phase of menstrual cycle among young, healthy women.

Materials and methods

Female volunteer students of Medical University of Gdańsk aged 19 to 30 were enrolled into the study. The exclusion criteria included pregnancy, use of hormonal contraception, menstrual disorders, cardiovascular and respiratory diseases and competitive sport activity. Each patient had 2 echocardiographic examinations of IVC diameter (d-IVC) and respiratory decrease in dimension in two time points: in the first days of menstruation (Phase M) and in the second part of cycle (Phase L). We estimated Phase L as 14 days before beginning of the next cycle. All examinations were conducted on fasting volunteers. The d-IVC was measured while supine, in the subcostal window and in longitudinal projection, 3 cm from the right atrium outlet (Figure 1). IVC diameter <2.1 cm was considered normal. Additionally, questionnaires concerning data about menstrual cycle characteristics (length, regularity, day of cycle during examination) fluid intake, amount of weekly physical exercise and anthropometrics were collected. Extended echocardiographic study was conducted in each volunteer with IVC abnormalities

Statistical analysis

All data were tabulated in MS Excel and analyzed using the standard Statistica v.12.0 package (StatSoft, Tulsa Inc., USA). Data with normal distribution (based on Shapiro- Wilk test) were compared with student's t-test. Non-normally distributed variables were compared with non-parametric test (Wilcoxson's test). Chi-squared test was used to analyze the number of cases between dichotomized subgroups. P-value <0.05 was considered statistically significant.

Results

31 volunteers completed the study. Average age was 23.7±4.2 years and BMI 20.97±2.4 kg/m2. There was a significant difference between the d-IVC in Phase M and Phase L (1.98±0.25cm vs 1.86±0.3cm, respectively; p <0.05; Figure 1). On the contrary, we did not observe that correlation in terms of the inspiratory collapsibility. In the Phase M 77% patients achieved at least 50% decrease in dimension during inspiration comparing to 87% in Phase L (p=0.89). Physical exercise time did not affect a d-IVC (1.9±0.36cm for >2.5 hours/week group and 1.87±0.23cm for ≤2.5hours/week group; p=0.74). Also, there was no difference in d-IVC due to the amount of fluid intake (1.9±0.42cm for ≥2liter/day group versus

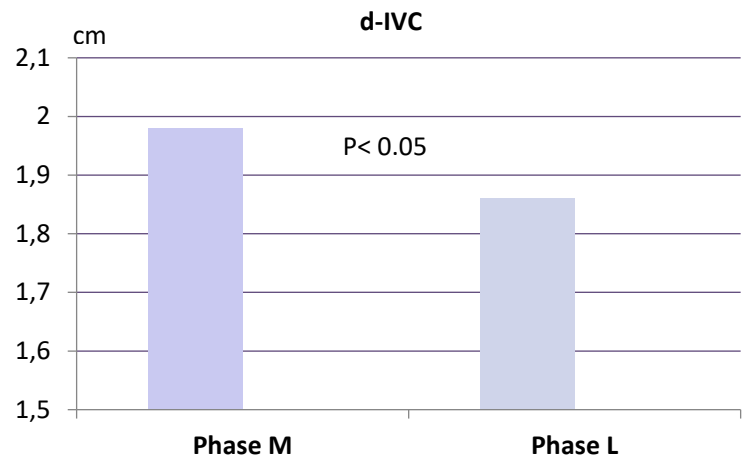

Figure 1. d-IVC depending on the phase of menstrual cycle

1.88±0.2cm for <2liter/day group; p=0.8). 35% patients had d-IVC exceeding reference values at least in one examination but full echocardiography did not reveal any other clinically significant abnormalities.

Discussion

As the availability of the right heart catheterization is limited, echocardiographic methods to assess right atrial pressure including IVC measurement are commonly performed. In several causes (e.g. athletic training, obesity or narrowing of the IVC-right atrium junction) IVC enlargement is observed in the presence of normal right atrial pressure [6]. Furthermore, the accuracy of IVC assessment depends on patient's body shape and also on examiner's technique [7-8]. In clinical practice, isolated IVC dilation may be noticed among patients without any other echocardiographic abnormalities [9].

There are several reports assessing the impact of the menstrual cycle on echocardiographic parameters. Changes in female sex hormones level may affect left ventricular diastolic function without significant influence on the right and left atrial volumes, left ventricular volumes and ejection fraction [10]. Our data show that in the population of young, healthy women, IVC diameter is dependent on the phase of menstrual cycle. First days of menstruation are associated with the larger dimension of IVC, which corresponds with the lowest level of vasodilatory sex hormones (estrogen, progesterone) during that phase [11-12]. We did not observe similar correlation with IVC respiratory variation and cycle phase. Those discrepancies may arise from the less repeatability of IVC respiratory collapsibility measurements. Accuracy of the IVC diameter assessment during inspiration can be affected by respiratory motion in the position of the IVC [13]. Interestingly, over one third of the studied group had d-IVC exceeding reference values at least in one examination as an isolated abnormality in echocardiography. Therefore, it seems to be justified to extend the diagnostics with a question about menstrual cycle phase.

Table 1. Studied group characteristics

Age (years)	23.7 ± 4.2	
BMI (kg/m²)	20.97 ± 2.4	
	PHASE M	**PHASE L**
d-IVC (cm)	1.98 ± 0.25	1.86 ± 0.3
Respiratory collapsibility (%)	65.1 ± 25.3	72.9 ± 25.3

Conclusions

Pilot results of our study shows that in the population of young women diameter of inferior vena cava exceeding reference values can be observed frequently. IVC dimension changes correspond with the menstrual cycle phases. However, it does not affect the IVC collapsibility during inspiration. The significance of this observation is not clear and requires further studies on larger groups.

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EUROPEAN JOURNAL OF TRANSLATIONAL
AND CLINICAL MEDICINE 2019;2(1):56-69

META-ANALYSIS

Late postoperative slippage of the cerebral aneurysm clip. A systematic review and meta-analysis

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Abstract

Background: A late clip slippage from the previously properly secured cerebral aneurysm is rarely observed. To date these complications have not pooled and evaluated using systematic review methodology. The objective was to report factors attributed to the late slippage of the aneurysm clip in the postoperative period. **Materials and methods:** All causes of postoperative clip slippage were systematically reviewed and analysed according to PRISMA Individual Patient Data protocol. Medline (PubMed), Embase, Cochrane, ISI Web of Knowledge and Google Scholar were searched for all relevant cases. **Results:** Systematic review of the literature yielded 105 original cases proving slipped clip in the postoperative period. The slipped clip caused bleeding in 53.8% of patients. The putative cause of clip slippage was provided in only 34.7% of the published cases. If a single clip was used, then complete clip slippage was noted more often (p=0.04). Multiple clipping and clip-wrapping techniques were postulated as ways to prevent postoperative clip slippage. **Conclusions:** The reason for late slippage of the aneurysm clip remains unexplained by most authors. Based on systematic reviewing, the use of tandem of clips prevents their late migration off the aneurysm. Clipping with wrapping or use of a single clip reinforced by any wrapping material seems a more durable solution.

Keywords: systematic review • intracranial aneurysm • clip slippage • neurosurgical clipping

Citation

Szmuda T, Słoniewski P. Late postoperative slippage of the cerebral aneurysm clip. A systematic review and meta-analysis. Eur J Transl Clin Med. 2019;2(1):56-69.
DOI: 10.31373/ejtcm/103442

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No external funds.

Available online: www.ejtcm.gumed.edu.pl

Background

Postoperative clip slippage is a rarely observed complication. Authors attributed this complication to the application of a short clip, some alloy features or clip closing pressure [1, 2]. Repetitive opening of the clip further reduces its closing forces [3-5]. Another factor is the so-called scissoring effect [6-9]. Various authors demonstrated the examples of late clip migration following seemingly successful operations [10-13]. Less than 1% of the postoperative angiograms show an insufficiently secured aneurysm or a rotated clip [14]. Authors demonstrated various techniques in order to avoid clip slippage, although their interests were focused on the particular operative environment. Hundreds of case reports that were never critically appraised. To date, cases of clip slippage have not been pooled and analysed using a validated systematic review methodology. We aimed to collect and summarize the existing literature about clip slippage phenomena using the reproducible and widely accepted PRISMA Statement methodology [15].

Methods and materials

After reaching consensus, the authors developed a detailed protocol [16]. One author searched (November 2017), selected the articles and extracted data. Online Medline, Embase, Web of Knowledge, Cochrane and Google Scholar engines were queried for phrase: 'aneurysm' AND ('clip' OR 'clipping') AND ('slip' OR 'slippage'). Duplicating records were removed using Mendeley Software (ver.1.17.10). Screening was based on titles and abstracts. We accepted original case reports, reviews, commentaries, expert opinions including animal, technical studies, PhD dissertations and patents. No limits in time of publication or language were applied. Google Translate website was used in case of abstracts and articles not in English. Following eligibility assessment, extensive searches for relevant references followed data extraction. Two types of data were deemed valid for further narrative synthesis of evidence: (1) descriptions of postoperative clip slippage and (2) intraoperative manoeuvres intended for prevention of a late slip-off phenomena. Raw data from each patient (Individual Participant Data method, IPD) were analysed as if all slippage occurrences belonged to an assumed single cohort. The evaluation was performed in accordance to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for IPD systematic reviews, which included search, eligibility, extraction, and reporting [17]. Publication bias was not assessed.

We used typical statistical methods for relevant comparisons: chi-square, t-test or Mann-Whitney U test. Probability value less than 0.05 was considered significant. Statistica v. 13.1 (StatSoft Co, Tulsa, OK; USA) and Prism (GraphPad Software, La Jolla, CA; USA) were used. IRB Committee in the institution of systematic reviews is exempt.

Results

The literature search yielded 3034 records, mostly identified via Google Scholar which explores full-texts for keywords. 'Slip' unrelated to cerebral aneurysm was the main exclusion criterion. Finally, 139 studies were included for the synthesis.

We found 105 original cases reporting late clip migration. In a half of the cases the slipped clip caused bleeding (53.8%; 43/80), half of which were fatal (23/43). A routine postoperative angiography revealed the incidental clip displacement in 32.5% of cases (26/80). Anterior communicating artery (n=15), internal carotid artery (n=21, including 2 blister-like), middle cerebral artery (n=12) and basilar artery (n=7) were commonly encountered locations. In majority of cases (65.3%; 62/95) the authors were not able to provide any reason for clip slippage. Others blamed the defect of clip material in 15 patients (16.0%) and persistent arterial pulsation in 6 (6.4%). Surprisingly, specific features of the particular aneurysm were attributed to only 5 cases of slipped clips (5.3%).

The published reports rarely included aneurysm size, usually only if the aneurysm was giant (85.0%; 8/10). In a quarter of the slippage cases more than one clip was applied (23.3%; 10/43). In 82.9% of cases (68/80) a clip completely slipped off the aneurysm dome. Aneurysm location (p=0.65), size (p=0.26), rebleeding as the first symptom (p=0.65), fatal rebleeding (p=0.89) and occurrence in postoperative DSA (p=0.52) were not related to the degree (complete or incomplete) of clip migration. On the other hand, complete clip slip-off was significantly more often encountered if a single clip was used (82.1% vs. 44.4%, p=0.04). Regarding the direction of slip, in 87.5% of reports the clip migrated off the aneurysm (87.5%; 70/80), whereas in 8 cases (11.4%) the clip was displaced down onto the parent vessel, causing cerebral ischemia in 3 patents (37.5%).

Out of the 139 studies, 78 (56.1%) provided at least one suggestion on how to avoid late clip migration. The most commonly suggested method was placing several clips instead of one (15.8%; 24/139), followed by applying of clip-wrapping technique (7.2%p; 10/139) and performing DSA shortly after clipping (4.3%; 6/139). The suggested preventive methods were location-specific, e.g. in case of blood blister-like aneurysm authors postulated placing clips parallel to ICA or clip-wrapping.

PRISMA-IPD Checklist of items to include when reporting a systematic review and meta-analysis of individual participant data (IPD)

→ **go to: https://ejtcm.gumed.edu.pl/files/54**

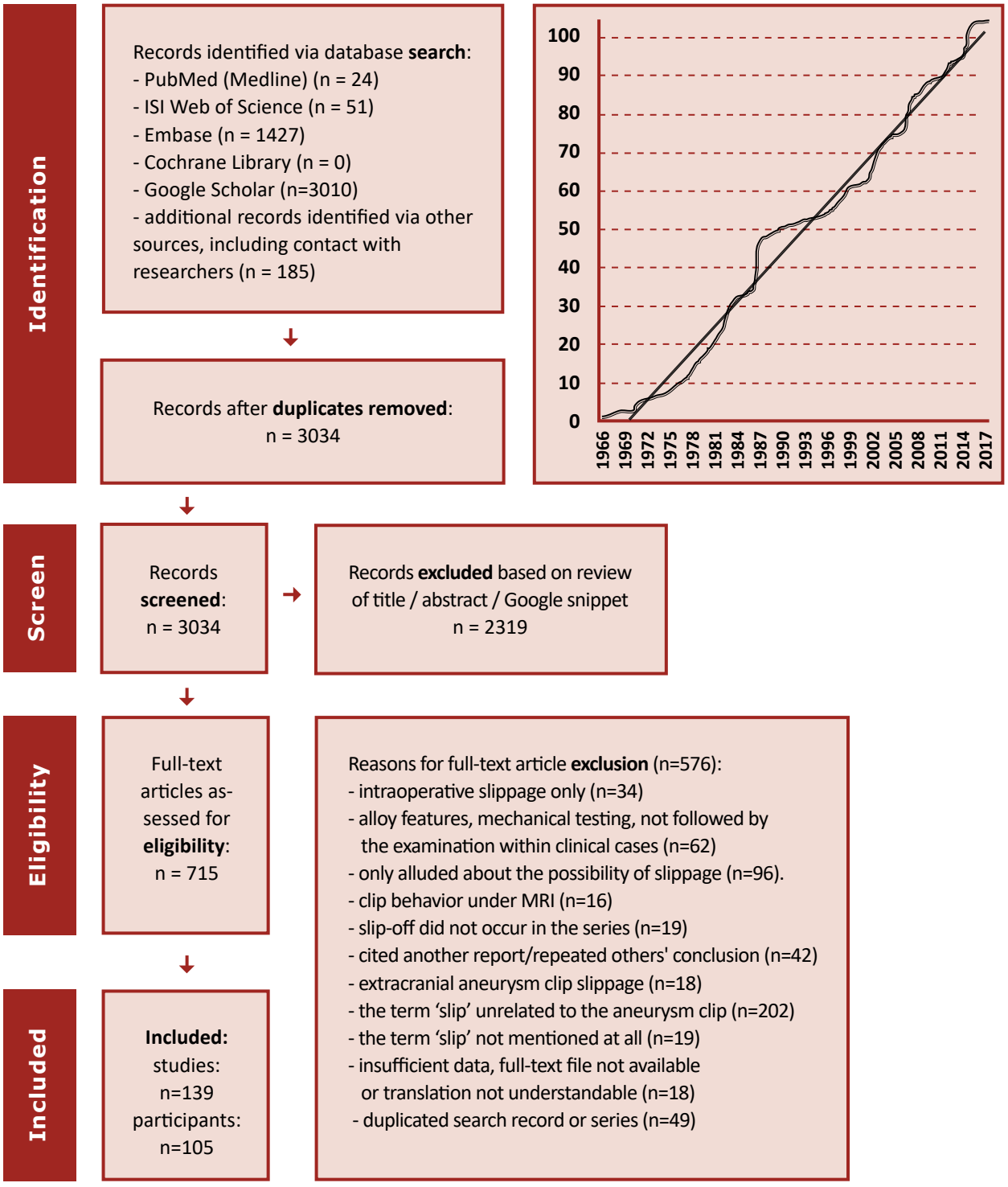

Figure 1. Flowchart depicting the strategy for literature search. Cumulative number of cases involving aneurysm clip slippage. The graph demonstrates the constantly increasing publication rate on this subject.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097.

Supplementary Table 1. Full table of studies included in the evidence synthesis.

No	Author	Year	Aneurysm location (size/other features)	Clip/s	Total/partial slip; direction of the slip	Suspected reason of slippage	Avoidance management	Diagnosis
MCA								
1	Matsumoto [1]	1987	MCA	unk	in	clip properties; authors presented a modified non-sliding clip, which blades closed at their tips.		MCA obstruction
2	Matsumoto [1]	1987	MCA	Yasargil	total; out			postop DSA
3	Matsumoto [1]	1987	MCA	unk	partial; out			oculomotor paresis
4	Edner [2]	1978	MCA	straight Heifetz	total; out	clip material fatigue	no filling of the aneurysm was confirmed on DSA.	head radiogram (1.5 y)
5	Nakayama [3]	1987	MCA	misused temporary clip	total; out	unk	none	rebleeding (1.5 mths)
6	Shigemori [4]	1987	MCA	unk	total; out	broad neck	none	unk
7	Hoh [5]	2001	MCA	unk	total; out	unk	none	rebleeding after 3 weeks
8	Asgari [6]	2003	MCA	1 Sugita	partial; out	unk	none	clip slippage not verified
9	Wester [7]	2009	MCA bifurcation	curved	total; out	low closing forces of the long clip	Instead of one long clip, multiple short clips should be used to reconstruct the artery.	fatal rebleeding (after closure of the wound)
10	Wester [7]	2009	MCA fusiform	3 unk	in (across the artery)	unk	none	infarction
11	Takahashi [8]	1987	giant MCA	Sugita	total; out		none	rebleeding (4 d)
12	Asgari [6]	2003	giant MCA	2 Sugita	partial; out	wide calcified neck; only distal 2/3 of clip grasped the neck	none	rebleeding
13	Pia [9]	1980	giant MCA	2 clips	total; out	unk	none	unk

ACoA								
14	Kandel [10]	1977	ACoA	unk	total; out	unk	none	unk
15	Czochra [11]	1980	ACoA	unk	total; out	unk	none	postop DSA
16	Sakurai [12]	1987	ACoA	clip and wrapping	total; out	unk	none	rebleeding (3 mths)
17	Haraoka [13]	1987	ACoA	encom-passing Heifetz	total; out	incompletely obliterated neck and pulsative forces to the neck over a long period	none	good recovery
18	Asgari [6]	2003	medium -sized ACoA	1 Yasargil Ti (Aesculap)	partial; out	should be differentiated with *de novo* aneurysm	none	rebleeding
19	Fukui [14]	2004	ACoA	unk	unk; out	unk	none	unk
20	Hayashi [15]	2004	ACoA	straight	total; out	clip head trap-ped between optic nerves	neurosurgeons	rebleeding (4 d)
21	Chen [16]	2009	ACoA	1 titanium	total; out	unk	none	rebleeding
22	Huh [17]	2012	ACoA	single clip reinforced by a booster clip	total; out	unk	none	rebleeding
23	Kunert [18]	2012	ACoA	unk	total; out	unexplained	none	control CTA
24	Takahashi [8]	1987	ACoA	clipping+-cyanoacry-late glue	total; out	selection of an inappropriate clip, inaccurate clip placement	none	fatal rebleeding (11 d)
25	Takahashi [8]	1987	ACoA	unk	total; out		none	rebleeding (17 d)
26	Yi [19]	2003	ACoA	bayonet standard Yasargil (Aesculap)	total; out	2 mm of neck remnant was supposed	none	postop DSA
27	Xuejian [20]	1998	ACoA	unk	total out	unk	none	fatal rebleeding
28	Yasui [21]	2004	giant ACoA	unk	in	the aneurysm was approached from interhemis-pheric approach	none	occlusion of parent artery; infarction

29	Izumo [22]	2013	A1	curved Ti	partial; out	unk	none	postop DSA
30	Iida [23]	2017	fusiform A1	straight	total; out	unk	none	rebleeding
ICA								
31	Skultety [24]	1966	ICA	unk	unk	unk	none	fatal
32	Sato [25]	1971	ICA	long, silver	total; out	presumably due to arterial pulsations	none	uneventful clinical course
33	Kariyattil [26]	2013	ICA	bayonet--shaped fenestrated Yasargil	partial; out	Intraop DSA is advised as revealed clip "scissoring effect" causing slippage after apparent right clipping.		
34	Edner [2]	1978	ICA/PCoA	straight Heifetz	total; out	clip head trapped between optic nerves	neurosurgeons	rebleeding (4 d)
35	Sengupta [27]	1978	ICA/PCoA	1 unk	total; out	unk	none	fatal rebleeding
36	Czochra [11]	1980	ICA/PCoA	unk	total; out	unk	none	postop DSA
37	Ebina [28]	1982	ICA/PCoA	Heifetz, then Sugita	total; out	unk	none	rebleeding
38	Horiuchi [29]	2012	ICA/PCoA	Yasargil titanium bayonet	in	scissoring effect	remove immediately scissor-like deformed clip	arterial occlusion (paresis)
39	Drake [30]	1973	board--based ICA/PCoA	1 Sundt	total; out	improper clipping; postoperative hypertension?	intraop and postop DSA; clipping under deep hypotension; clip should be fenestrated or occludes partially the arterial lumen.	clip slipped two times
40	Ikezaki [31]	1987	2 ICA/Opth	tandem of angle fenestrated	partial; in	unk	The blades should be applied parallel to ICA lumen	ICA stenosis
41	Drake [32]	1984	ICA/Opth	1 Sundt	total; out	unk	postop DSA	rebleeding
42	Hatanaka [33,34]	1987	ICA/Opth	unk	total; out	unk	glue applied on the clip spring	rebleeding

43	Melo [35]	2002	giant ICA/ Opth	unk	total; out	weak clip closing pressure	do not resterilize clips; repeat other suggestions to prevent slipping	postop DSA (8 mths)
44	Huh [36]	2011	paradinoid ICA	unk	in	unk	none	ICA occlusion
45	Nemoto [37]	1999	paradinoid ICA	2 clips	total; out	unk	none	postop DSA
46	Heros [38]	1983	giant paraclinoid ICA	unk	total; out	the reinforcing clip blades ruptured the sac while slipping	partial neck clipping with single clip even reinforced by another one should be avoided.	fatal rebleeding
47	Szmuda [39]	2012	giant ICA	2 straight, 1 bayonet Yasargil.	partial; out	weak closing forces of the clip and its resterilisation.	place several clips or stack one on the top of another can prevent clip slippage.	postop DSA
Blood blister-like ICA								
48	Diraz [40]	1993	ICA (BBA)	unk	total; out	due to brain retraction release	Embedding the clip by tearing a small	unk
49	Park [41]	2007	ICA (BBA)	unk	total; out	unk	none	postop DSA (5 wks)
50	Kuroda [42]	2016	ICA (anterior wall)	1 bayonet	total; out	radiation -induced severe	none	postop DSA (5 wks)
BA								
51	Melo [35]	2002	BA	unk	total; out			loss of consciousness
52	Miyachi [43]	1999	BA	unk	total; out	unk	none	postop DSA
53	Peerless [44]	1988	BA	unk	total; out	high arterial pressure	use multiple tandem clips; use clips with short blades to enhance clo- sing pressure.	rebleeding (8 y)

54	Drake [32]	1984	BA	1 Sundt	total; out	unk	postop DSA	fatal rebleeding
55	Carlotti [45]	1996	BA	unk	unk	unk	none	fatal rebleeding
56	Drake [46]	1996	large BA	unk	partial; in	neck shape	none	clip blades stenosed the origins of SCA; ischemia
57	Silverberg [47]	1981	giant BA	unk	unk	unk	apart from slippage, the aneurysm has thrombosed.	postop DSA
VA								
58	Suzuki [48]	1979	VA	unk	total; out	use an adhesive to prevent slippage; in case of slippage risk, optional to clipping is inserting copper wires to facilitate aneurysm thrombosis; postop DSA is essential; clips should cause a trauma to initiate intima healing within its blades.		fatal rebleeding (2 wks)
59	Takahashi [49]	1981	VA	unk	unk	unk	none	fatal rebleeding
60	Fukasawa [50]	1998	dissecting VA	unk	unk	unk	none	unk
61	Haraoka [51]	1999	middle third VA	unk	total; out	unk	none	fatal
PICA								
62	Drake [46]	1984	PICA	older clip	total; out	unk	none	fatal rebleeding
63	Oyesiku [52]	1986	PICA	Heifetz	total; out	The clip migrated to cauda equine (L3-4). "Force of returning brain" has been suggested as a factor of slippage.		low back pain with radiculopathy
64	Porchet [53]	1995	PICA	1 unk	total; out	unk	none	rebleeding
65	Kang [54]	2004	PICA	unk	unk	unk	endovascular embolization	postop DSA 5 days postop
66	Kim [55]	2009	PICA	3 Yasargil (straight, fenestrated, angled)	total; out	The angled clip migrated to sacral (S1) subarachnoid space. The reason of slippage is unknown.		low back pain

Other locations								
67	Kanai [56]	1992	hypoglossal artery	straight	partial; in (artery obliteration)	too large aneurysm for clipping or clivus proximity	consider endovascular approach	fatal rebleeding
68	Mann [57]	1984	pericalosal artery	unk	total; out	partial thrombosis of aneurysm	contralateral approach may limit slippage.	postop DSA
69	2005	orbito-frontal	straight Yasargil	partial; out	total; out	initial clipping occurs insufficient if rupture is proximal to parent artery; even 2 mm slippage can cause haemorrhage recur.		rebleeding (5 wks)
Unspecified location								
70	Drake [59]	1967	1 unk	unk	total; out	a clip incompletely occluding fundus with coexisting pulsations	coating a residual sac together with a clip and parent vessel.	unk
71	Troupp [60]	1971	1 unk	unk	total; out	unk	none	fatal
72	Gillingham [61]	1979	2 unk (1.1% of series)	Mayfield	unk	unk	none	fatal
73	Guidetti [62]	1970	1 unk	Mayfield	unk	unk	none	fatal rebleeding after 8 hours postop
74	Higuchi, [63,64]	1988 2003	unk	unk	total; unk	unk	none	fatal rebleeding
75	Hillman, Loach [65,66]	1976 1988	unk	unk	total; unk	unk	none	fatal rebleeding
76	Martin, Niikawa [67,68]	1990	unk	unk	total; unk	unk	none	postop DSA
77	Jimbo [69]	1997	1 unk	unk	unk	unk	In severe atherosclerosis the reinforcement with Surgicel® or Biobond® can prevent from slippage.	unk
78	Kano, Troupp, Wermer [60,70,71]	1971 2005 2007	1 unk	unk	unk	unk	unk	unk

79	Park [72]	2014	8 unk (4 atherosc-lerotic, 4 non-athe-rosclerotic)	unk	unk	sliding of the clip due to atherosclerotic neck	use multiple clips	unk
80	Nievas [73]	2007	7 cases	unk	total; out	unk	none	postop DSA
81	Shephard [74]	1983	4 cases; unk aneurysms	unk	unk	unk	none	fatal rebleeding
82	Sugita, [75]	1976	unk	Heifetz	unk	unk	broad-necked aneurysms should be secured by clips with more than 80 gm clo-sing pressure.	postop DSA
83	Sundt [76]	1982	unk	Heifetz	unk	unk	none	unk
Proposed management aimed for prevention of further clip slippage								
84	Iwama [77,78]	2004	large M1	Dome puncture prevent slipping in or out of aneurysm clip				
85	Yasargil [79]	1974	distal ACA	Coagulation of the neck produces a smaller neck, then less chance of clip slipping.				
86	Ohno [80,81]	1992 1999	ICA, ACA	Sugita straight booster clip was used for preventing a slip-out of the first clip.				
87	Sasaki [82]	1991	ICA	In giant aneurysms additional clips should be applied to prevent first clip slippage.				
88	Inci [83]	2015	ICA	more long clips were placed parallel to the first clip on calcified-necked aneurysm				
89	Hashimoto, Kato [84,85]	1997 2009	ICA	"interlocking" the tandem of angled fenestrated clip blades reinforce their closing pressure and thus reduces the likelihood of slipping.				
90	Ohmoto [86]	1991	cavernous ICA	reinforcing (booster) straight clip was used in wide-necked aneurysm				
91	Uemura [87]	1987	paraclinoid ICA	For prevention of Sugita clip slipping, **a small piece of dura is laid between the spring and sphenoid** with coating.				
92	Kataoka [88]	1995	paraclinoid ICA	**cortex splitting to adjust a clip spring** to prevent slippage.				
93	Gianotta [89]	1994	ICA/Opth	Clip slip off the aneurysm is frequent in ICA/Opth; to avoid slippage series of clips should be stacked one on of top of another.				
94	Sengupta [90]	1979	ICA bifurcation	aneurysm sac was aspirated shortly after clipping to prevent further slippage				

95	Fujioka, Shigeta [91,92]	1992 2003	ICA (BBA) or dissecting	"clip on wrapping" method to prevent either intra- or postop slippage
96	Kato, Nakagawa, Osawa [93–95]	1986 1991 1993	ICA (BBA)	"Clipping on wrapping" with/without applied on cellulose fabric to prevent slippage.
97	Kazumata [96]	2014	ICA (BBA)	Radial artery to MCA bypass graft is advocated decreases the risk of postop slippage.
98	Yoshimoto [97]	1996	ICA (BBA)	wrapping with muslin gauze may prevent slipping.
99	Otani [98]	2009	ICA (BBA)	right-angled clip blades placed parallel to the parent artery prevent slippage
100	Mooney [99]	2015	ICA (BBA)	placing a thin layer of cotton reinforcement beneath the clip blades
101	Brown [100]	2017	ICA (BBA)	clip blades should be placed along the axis of ICA
102	Drake [46]	1996	BA bifurcation	In order to prevent further clip slipping down and stenosing/kinking the P1 origins, a Drake proposed the tandem clipping, composed of one fenestrated and one straight clip.
103	Hirikoshi [101]	1997	BA bifurcation	If clip blades slip toward BA closing the PCA origins, direct clipping should be abandoned.
104	Fujitsu [102]	1994	VA, BA	"wrap-clipping" technique with Dacron-meshed silastic sheet
105	Sano [103]	1997	dissecting VA	a second curved fenestrated booster clip was placed on blades of the first clip to eliminate its further slippage.
106	Hylton [104]	1988	giant	atheroma removal from aneurysm sac should precede direct clipping
107	Welch [105]	1997	giant	intraaneurysmal thrombus prevents clips from closing and force the clip onto the parent artery; partial thrombectomy while temporary clipping is advised.
108	Wellman [106]	1998	giant	clips placed across the neck require total occlusion, otherwise a pulsating aneurysm neck pose a risk of slipping away or inwards.
109	Kawai [107]	1987	giant	To prevent slipping-in of the clip and artery occlusion, the dome thrombectomy, neck thrombarterectomy, also using CUSA should follow neck clipping.
110	Lawton [108,109]	1994 1999	giant	intraaneurysmal thrombus prevents clips from closing and force the clip onto the parent artery; partial thrombectomy while temporary clipping is advised.
111	Symon [110]	1992	giant	debulking the aneurysm and collapsing its neck diminish the risk of clip slippage toward parent artery.
112	Nakamura [111]	2012	wide-necked	multiple clipping to prevent clip slip-out.
113	Nakano [112]	2000	wide-necked	"Clipping on wrapping" to prevent slip off.
114	Turkmani [113]	2015	aneurysms with a calcified neck	a single clip can slip downward at the calcified neck thus a clip reconstruction should be employed
115	Kato [114]	2012	previously coiled	Specific features of sac and neck of previously coiled aneurysm should be considered preoperatively in order to avoid further slippage.
116	Kiran [115]	2015	very small	double-clip technique (two parallel mini clips) prevents from slipping

117	Giannotta [116]	1995	4 unk	Clip slippage was attributed to older style clips or their improper placement. Recommended preventions: large portion of sac should be dissected first, otherwise clip closing forces would not counteract tethering of fibrous material; multiple and tandem clipping; use of booster clips; evacuating the sac; puncture the sac once neck clipping is complete; do not place clips under hypotensive anaesthesia.
118	Kato [117]	1995	unk	Fenestrated clip itself prevents slippage.
119	Guo [118]	2007	excising a sac may contribute to a clip slippage	
120	Hollin [119]	1973	persistence of blood pulsations to the clip	
121	Hori, Iwata, Kato, Kodama, Lee, Mizoi, Sugita [120–127]	1976 1979 1982 1987 1988 1997	additional wrapping/coating or adhesive (i.e. cyanoacrylate) use to prevent further slippage.	
122	Mayfield [128]	1971	Clip blades should be parallel and incorporate as little of the surrounding tissue as possible.	
123	Nievas [129]	2000	Developed several tips to prevent clip slippage: use the mobile fulcrum clip, reduce the amount of sac filling (decrease blood pressure or use a temporary clip), place a second occluding clip parallel to the first one (then correct the first clip), never use a clip that has been left open in the instrument or resterilized for a subsequent operation, leave a depth of at least 2 mm from the tip, resect completely the arachnoid bundles surrounding the aneurysm neck, remove the atheroma before a clip is applied on the ruptured ICA aneurysm, perpendicular clip insertion may lead to blades' cross, the neck resistance should be verified prior to clip placement.	
124	Nishi [130]	2007	Wrap-reinforced clipping for slippery aneurysm neck; sequential clip placement to avoid slipping-in and occluding parent vessel (a pilot clip is removed after stabilizing a second clip).	
125	Nussbaum [131]	2010	The modified fenestrated clip ("compression clip") was introduced to avoid slipping from atheromatous, thrombotic or previously coiled aneurysms.	
126	Origitano [132]	1997	Puncture the sac and perform postop DSA to avoid slippage phenomena.	
127	Sano [133]	1991	A double-secured aneurysm closure - fenestrated and straight clips closed across the neck; that combination of clips initiated by Charles Drake.	
128	Schmid -Elsaesser [134]	2000	broad-based aneurysms should be secured by more than one clip.	
129	Sughrue [135]	2011	incorporating pathological tissues at the neck that can cause clip slippage	
130	Sugita [136]	1985	If a clip slips onto the parent artery and causes stenosis, puncturing the sac is indispensable. Placing a second clip prevent slipping, even though the first clip do not open with arterial pulsation. Total wrapping after even successful clipping may prevent postop slipping. Putting some chemical adhesives on clip blades.	
131	Sundt [137]	1984	applying a booster clip prevent from slipping	
132	Safavi-Abbasi [138]	2016	cotton-clipping and cotton-augmentation strategies	
133	Sakata [139]	2015	clip and wrap technique using Gore-Tex sling	

References to supplementary Table 1. → go to: https://ejtcm.gumed.edu.pl/files/53

Discussion

Our systematic review was divided into two stages: we pooled all valid cases in which an aneurysm clip slid off and collected all studies addressing prevention of clip slippage. By including every type of study into the systematic review, we intended to reveal case reports and authors' own experiences. However, most authors (65.3%) did not provide any reason why the clip slipped off. The incomplete clipping and insufficient amount of used clips were the most commonly stated reasons. On the other hand, tandem clipping seems more durable option proposed by 15.8% of authors in our systematic review [9, 18-20].

The prevention of clip slippage depended on aneurysm location. Specifically, reinforcing with any wrapping material, clip-wrapping methods and placing blades parallel to carotid were proposed in blood blister-like aneurysms [21-25]. Whereas in cases of a clip slipped from ACoA aneurysm, the authors did not provide any suggestions for repair.

Our systematic review pooled reports of slipped cerebral aneurysm clips. Based on this cohort we concluded that by using a single clip the surgeon should consider aneurysm recurrence. It was often speculated in the literature that multiple clipping more seems to be a more durable solution. Plenty of valuable hints on how to avoid postoperative clip slippage were suggested in the literature and we listed all of them based on the specific aneurysm location.

Ethical approval

Formal consent is not required for this type of study.

Informed consent

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

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EUROPEAN JOURNAL OF TRANSLATIONAL
AND CLINICAL MEDICINE 2019;2(1):70-77

REVIEW ARTICLE

Cardiovascular and metabolic side effects of second-generation antipsychotics – narrative review

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Abstract

Since their introduction, the use of second generation antipsychotics (SGAs) has extended far beyond schizophrenia. With the increased usage of these agents, particular attention has been paid to their metabolic and cardiac side effects. This narrative review is an attempt to briefly summarize the conclusions from recently published systematic reviews on cardio-metabolic side effects of SGAs. Although no SGA is entirely free of these adverse effects, there are major differences in their prevalence between the specific medications. Numerous studies demonstrated particularly unfavorable side effect profiles of olanzapine and clozapine. The lack of conclusive data is a major limitation for many studies, particularly in the pediatric population. In this article we also discussed the meanings of these findings, suggested cardio-metabolic screening during SGA treatment and side effect management strategies.

Keywords: metabolic side effects of drugs • neuroleptics • review literature • drug-related side effects and adverse reactions

Citation

Waszak PM, Piskorska NA, Sarbiewska M, Zagożdżon P, Cubała WJ. Cardiovascular and metabolic side effects of second-generation antipsychotics - the narrative review. Eur J Transl Clin Med. 2019;2(1):70-77.
DOI: 10.31373/ejtcm/104363

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No external funds.

Updated: 2023-12-11

Available online: www.ejtcm.gumed.edu.pl

Introduction

Since the introduction of second generation of antipsychotics (SGAs) in the 1990's, their indications have expanded beyond schizophrenia and include other disorders with psychotic symptoms, e.g. bipolar disorder or psychotic depression. More recently, increasing off-label prescribing of SGAs has been noted for the treatment of non-psychotic disorders, e.g. obsessive–compulsive disorder, personality disorders, anxiety disorders as well as child and adolescent mental health disorders [1-2].

There is a growing concern that with increased prevalence of treatment with antipsychotics, their side effects will also become also more prevalent [1]. The older first-generation antipsychotics (FGAs) were tolerated by only a limited group of patients, therefore SGAs were designed to have less harmful, at least with regard to extrapiramidal symptoms [3]. However, many studies have shown that SGA use is associated with significant risk of side effects outside the central nervous system, e.g. cardiovascular events (myocardial infarction, cerebral stroke) and metabolic disease (type 2 diabetes, weight gain) [3]. From the practical point of view, the above-mentioned risks should be assessed together instead of separately [4]. In recent years, more attention has been paid to the incidence of the above-mentioned disorders in drug-naïve or untreated individuals with severe mental disorders [5]. This may also suggest their intrinsic susceptibility to cardio-metabolic consequences and can be regarded as risk factor itself [4].

Well-established treatment effectiveness of SGAs, without comparable alternative treatment options, pushes mental health professionals to still rely on these drugs. Thus, there is a need for highest-quality scientific evidence to make the appropriate clinical decisions regarding treatment with antipsychotics. The purpose of this article is to provide a brief and practical overview of SGAs' cardio-metabolic side effects, based on the recently published meta-analyses and systematic reviews.

Materials and methods

This is a narrative type of review. Independent English-language literature search has been done by two first authors (PMW, NAP) was done on the 15th of November 2018, using the Scopus, Google Scholar and PubMed databases. We used a query containing title keywords "atypical" OR "second generation" AND "antipsychotics" AND "systematic review" combined with appropriate set of keywords from the particular topic of our interest e.g. weight gain, diabetes, metabolic syndrome, dyslipidemia, cardiovascular events (myocardial infarction, cerebral stroke) and child and adolescents mental health. A detailed cross-review of references was also carried out if necessary. We focused mainly on articles published in the last five years. Exclusion criteria were: non-clinical laboratory research, single-drug studies, articles analyzing assessment and management of SGAs side effects. Due to narrative format of this review, no statistical calculations were performed.

Results

Weight gain

Weight gain is the side effect of antipsychotic treatment most frequently observed by patients. Furthermore, weight gain is also the most frequently analyzed variable in studies on the metabolic effects of antipsychotics. A large meta-analysis that included more than three hundred studies, revealed that almost all antipsychotics cause weight gain, especially in case of prolonged use (defined as >38 weeks) [6].

Olanzapine and clozapine were the most significantly associated with weight gain, while risperidone was less frequently reported in the analyzed studies [7]. In detail, clozapine was associated with the greatest risk of weight gain, with a high rate of >10% increase above the original body weight. To make matters worse for the patients, there is no convincing evidence that they will stop gaining weight stop once the SGA is discontinued [7]. No drug caused weight loss, whilst amisulpride, aripiprazole and ziprasidone were associated with no significant weight change [6].

Metabolic syndrome

The data from systematic review and meta-analysis suggest that patients receiving antipsychotics are at higher risk of metabolic syndrome, compared to those who are antipsychotic-naïve. The prevalence of metabolic syndrome is significantly higher with clozapine (47.2%, 95% CI:42%-52.6%;), followed by olanzapine and quetiapine; (36.2%, 95% CI: 31.8%-40.9%) and 37,3% (37.3%, 95% CI:24.7%-47.8%) respectively. Patients treated with aripiprazole had lower odds of metabolic syndrome compared to other medications (19.4%, 95% CI:8%-34,2%) [8].

Type 2 diabetes

In a systematic review of the literature on population-based studies of SGA and metabolic dysfunction,

Hirsch et al. found strong association of using olanzapine and type 2 diabetes (T2DM) with seven out of nine studies showing correlation between olanzapine and this adverse event [9]. Also clozapine seems to carry greater risk of diabetes with three of four studies showing this association. The evidence was equivocal for risperidone and quetiapine, indicating that further research is needed to define relationship between other SGAs and T2DM [9].

Dyslipidemia

Dyslipidemia has rarely been analyzed in population studies. In the few published studies, SGAs were compared to heterogeneous substances (e.g. placebo, antidepressants) and non-uniform measurement methods were used (e.g. lipid profile, co-prescirbed lipid-lowering drug). Olanzapine and clozapine also appear to be strong risk factors here, although the data is highly inconclusive. Aripiprazole may also be associated with dyslipiedemia, while risperidone appears to be unrelated or even protective [9].

Hypertension

We identified only one systematic review which analyzed the association between treatment with SGAs and hypertension. It showed significant association between hypertension and olanzapine, quetiapine and ziprasidone treatment, while aripiprazole and risperidone were not associated with increased blood pressure [9].

Children and adolescents

The pediatric population is a special group due to the possible influence of drug side effects on further organ development. As noted earlier, the use of antipsychotics, especially SGAs, has significantly increased in this population. We adopted age criteria defined by Pillay et al. 2018, (≤24 years) [10].

In the pediatric population, SGAs have been shown to have a stronger effect on weight gain compared to FGAs. Metabolic complications were significantly more frequent in the SGAs than in the placebo/no treatment groups. In general SGAs caused 0.043 kg weight gain [95% CI, 0.015 to 0.072] per week of additional treatment [10]. The Network Meta-analyses for Body Composition comparison Outcomes compared the effects for individual drugs. The use of olanzapine was associated with the largest increase in body weight - an average of 4.12 kg (of BMI 1.51 kg/m^2). Whereas risperidone (1.85 kg), quetiapine (1.25 kg) and aripiprazole (0.88 kg) have respectively milder effects. The other drugs' studies did not have consistent results. Majority of the above results were drawn from studies with short follow-up (6-12 weeks). There were no significant dose-dependent differences in weight gain (Aripiprazole 15/30 mg /d vs. 10 mg /d; Asenapine 10 mg /d vs. 5 mg /d; Quetiapine 600/800 mg /d vs 400 mg /d) [10].

In the short-term, there were no differences in the occurrence of a pathologically prolonged QT interval between the SGAs and placebo administered groups [11]. Studies on serious complications have low levels of evidence, mainly due to small study samples secondary to the rarity of their prevalence. Studies on dyslipidemia and hyperprolactinemia were also characterized by equivocal results and frequently insignificant p values. However, in subgroup analysis, quetiapine and risperidone may increase serum prolactin more frequently in females than in males [10].

Compared to placebo, patients treated with any SGA for >1 year may have an increased risk of diabetes, 7.8 vs. 25.3 cases per 10,000 person-years follow-up (HR, 2.89, 95% CI, 1.64 to 5.10) [12]. What is important, this effect may persist up to one year after discontinuation of treatment (at least for the drugs tested in this analysis - risperidone, olanzapine, aripiprazole, quetiapine, and ziprasidone) [12]. Further large, observational studies are highly needed.

QTc prolongation

It is well-known that drug-induced changes in the QTc (Corrected QT Interval) can cause severe cardiac arrhythmias, including sudden cardiac death. In an extenstive review, Hasnain & Vieweg (2014) did not find a clear link between drug-related QTc prolongation and Torsade de pointes and instead the authors draw attention to a much larger share of other QTc prolongation risk factors [13]. Due to inconsistent evidence, no attempt was made to stratify the risk of QTc prolongation depending on the SGA used, with exception to sertindole which causes statistically and clinically significant prolongation of the QTc interval [13]. Similarly, „limited but emerging data" showed potential association of iloperidone, clozapine, ziprasidone and quetiapine can cause prolonged QTc interval, while olanzapine and risperidone have modest effect [13]. Data from a systematic review of poly-pharmacotherapy confirm that the combination of these drugs may result in a clinically significant prolongation of the QTc interval [14].

Cerebrovascular and cardiovascular events

Schizophrenia itself is associated with a higher incidence of stroke, cardiovascular disease, congestive heart failure, and might also increase the risk of coro-

nary heart disease [15]. Because of their direct correlation with mortality, cerebrovascular incidents have a special clinical position among the analyzed adverse drug effects. The conclusions from a systematic review underline increase in the risk of cerebrovascular events in patients receiving any antipsychotic drug (OR 1.45; 95% CI 1.24-1.70) [16]. In subgroups analysis, particularly high risk has been reported in patients using FGAs (OR 1.49 95% CI 1.24-1.77). Slightly smaller, though not statistically significant, increased risk was reported for SGAs (OR 1.31, 95% CI 0.74- 2.30). The authors emphasize the significant divergence of component test results. In addition, the use of any antipsychotics in patients with dementia was associated with only a moderate increase in cerebrovascular event risk (OR 1.17, 95% CI 1.08-1.26) [16].

The use of any antipsychotic drug increased the risk of acute myocardial infarction compared to placebo (OR 1.88, 95% CI 1.39, 2.54) [17]. The analysis showed a divergence of this risk between FGAs (OR 2.19, 95% CI 1.46, 3.28) and SGAs (OR 1.72, 95% CI 0.96, 3.07). In one of the included studies, a significant increase in the risk of acute myocardial infarction was associated with the use of amisulpride (OR 5.65, 95% CI 2.97, 10.76) [17]. The subgroups analysis showed a significantly increased risk in patients with schizophrenia (OR 2.48, 95% CI 1.66, 3.69) and dementia (OR 1.82, 95% CI 1.16, 2.84). When the duration of treatment was analyzed, there was a significant reduction in the risk of acute coronary syndrome over time, with an odds ratio of 2.64 (95% CI 2.48, 2.81), 1.59 (95% CI 1.17, 2.18), 1.35 (95% CI 1.09, 1.67) respectively on 30 to 60 and 90 days since the beginning of antipsychotic treatment [17].

Discussion

When managing pharmacological treatment, clinician should always have in mind the potential adverse effects of prescribed drugs, because their occurrence may complicate the treatment outcome. Patients with mental illness, particularly those suffering from schizophrenia, have many risk factors for discontinuation of treatment, including lack of awareness of illness, psychoactive substance abuse and also drug-related complications [18].

Severely mentally ill patients have a substantially shorter lifespan (10-20 years) than the general population. Despite the advances in research and health care, this life-expectancy reduction is actually increasing [19]. Among schizophrenia patients, the coexistence of diabetes is significantly more frequent than in the general population, while the increased risk of cardiovascular diseases contributes significantly to the premature mortality of these patients [16,20]. Majority of cardio-metabolic side effects of SGAs are chronic and not obviously visible to patients at the very beginning of the treatment, while leading to excessive mortality. Thus, more intensive screening is recommended for patients receiving SGAs [5]. In fact, as shown by population studies, compared to those who have cardiovascular disease only, patients suffering from schizophrenia and cardiovascular disease face significant disparities in treatment e.g. less frequent referrals to specialists, fewer laboratory cholesterol tests or limited access to cardiac surgery procedures [21].

Recent evidence suggests that the incidence of cardiovascular diseases among people with severe mental illness is not only affected by antipsychotic treatment. To investigate this, more and more studies were carried out on patients who were untreated, during their first episode of the disease or with a high risk of developing psychosis. Data from systematic reviews on the first episode of psychosis confirmed the association of SGA treatment with insulin resistance, impaired glucose tolerance and elevated triglicerydes, without elevations in fasting plasma glucose, total and low-denisty lipoprotein levels [6,22-23]. All this may suggest a more complex, multifactorial nature of cardio-metabolic complications in severely mental ill patients. Simply put, the risk of developing diabetes in a patient suffering from schizophrenia is defined as 50% dependent on traditional risk factors plus an additional increase in the total risk by 2-3 times [24]. Treatment with any antipsychotic drug increases this risk by a further 10%, with a mere 2% difference in risk between FGAs and SGAs [24].

An appropriate monitoring program for cardiovascular and metabolic risk factors for patients treated with antipsychotics has been established. Current European recommendations on monitoring and decision-making are based on the consensus of three scientific associations (European Psychiatric Association, European Association for the Study of Diabetes and the European Society of Cardiology) and are summarized in Table 1 [5]. Perhaps an even more frequent assessment should be adopted for patients with additional risk factors and/or those treated with drugs that are most associated with side effects: olanzapine, clozapine.

Interventions to manage the occurrence of individual side effects have also been tested. The first-line intervention is reducing the dose or changing the antipsychotic drug. In many cases this is a sufficient strategy [25]. Then, head to head comparisons are particularly useful at supporting the decision-making process when switching the pharmacologic agent and such analysis is summarized in Table 2 [26]. Unfortunately for some patients, a switch of the drug is associated with an unacceptably high risk of exacerbation of psychosis. Remaining medical interventions should focus on the proper

Table 1. Recommendations for metabolic risk factor monitoring in patients with severe mental illness or on antipsychotic medication (based on [4])

Routine monitoring	Timing of assessment	Treatment decisions
Personal and family history of diabetes, hypertension, coronary heart disease (myocardial infarction or stroke)	At baseline, at 12 months, and at least annually thereafter*	Choice of antipsychotic agent Switch medications
Smoking, exercise, dietary habits	At baseline, 6 weeks, 3 months, 6 months, at 12 months and at least annually thereafter*	Smoking cessation
Height and weight (BMI)	At baseline, 6 weeks, 3 months, 6 months, at 12 months and at least annually thereafter*	Behavioral interventions for obesity or prediabetes
Waist circumference	At baseline, 3 months, at 12 months and at least annually thereafter*	Behavioral interventions for obesity or prediabetes
Blood pressure	At baseline, 3 months, 6 months, at 12 months and at least annually thereafter*	Behavioral interventions for obesity, antihypertensive treatment
Fasting plasma glucose	At baseline, 6 weeks, 3 months, 6 months, at 12 months and at least annually thereafter*	Behavioral interventions for obesity and prediabetes, oral antidiabetes drugs
Fasting lipid profile	At baseline, 6 weeks, 3 months, 6 months, at 12 months and at least annually thereafter*	Behavioral interventions for obesity and dyslipidemia, lipid-lowering medication
Electrocardiographic parameters5	At baseline**	Referral (external or internal)

***This frequency of assessment assumes that baseline results were normal; more-frequent follow-up is recommended for patients with abnormalities and those with cardiovascular and metabolic risk factors.**

****Desirable for all patients, but only required in those with cardiac risk factors. Follow-up electrocardiography is conducted as needed to assess baseline abnormalities or new symptoms, especially palpitation at rest and without anxiety, arrhythmia, dizziness or syncope upon exertion.**

treatment (by an appropriate specialist) of developed hypertension, dyslipidemia, hyperglycemia, diabetes and tobacco cessation [5]. Lifestyle changes have also been studied in the population of patients treated with SGAs [24, 27].

New directions in research focus on adjunct drugs (e.g. metformin, topiramate, aripiprazole) to correct the cardiovascular and metabolic side effects of SGAs [5, 27]. By reducing insulin resistance, metformin has the most proven evidence of efficacy in reducing antipsychotic-related weight gain [27]. Aripiprazole has its advantage due to additional antipsychotic action, while lowering the lipid level and therefore reducing weight on average by 2,13 kg compared to placebo [27]. Topiramate has been proven so far that it effective in diminishing only the olanzapine-induced weight gain by 4,4kg on average [27].

Table 2. General summary on antipsychotics cardiovascular and metabolic side effects (based on [3,8,24])

Adverse effect	Weight gain	Metabolic syndrome	Increase in QTc interval	Cardiovascular events (myocardial infarction and stroke)	Hyper-cholesterolemia
Amisulpride	0/+	0/+	0/+	++	0
Aripiprazole	0	0/+	0/+	0/+	+
Asenapine	+	0/+	0/+	+	0
Brexpiprazole	0	0/+	?	0/+	+
Cariprazine	0/+	0/+	?	?	0/+
Clozapine	+++	+++	++	++	+++
Iloperidone	+/++	+	++	?	++
Lurasidone	0/+	0/+	?	?	0/+
Olanzapine	+++	+++	+	++	+++
Paliperidone	++	+	+	+	+
Quetiapine	++	++	++	++	++
Risperidone	++	+	+	++	0
Sertindole	++	+	+++	0/+	+
Ziprasidone	0/+	0/+	++	+	+

Notes: +, ++, and +++ indicate comparative, not absolute, and side effect relevance among drugs. ? indicates no evidence available.

The major limitation of this review is its mainly narrative character, without possibility to employ systematic approach to collecting evidences and statistical analysis. To overcome this limitation, we decided to base our study on recent systematic reviews, a category considered the highest degree of evidence in medical sciences. Unfortunately, most studies still lack data on long-term effects. Also in some subgroups (e.g. the pediatric population) there is a lack of conclusive data on the most significant endpoints (e.g. particular drugs' association with cardiovascular events).

Conclusions

This short summary may help to understand the importance of cardio-metabolic side effect during SGAs treatment. This review brings together what is currently known about these risks. Further large and prospective long-term studies are needed to fill existing gaps in knowledge.

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EUROPEAN JOURNAL OF TRANSLATIONAL
AND CLINICAL MEDICINE 2019;2(1):78-84

REVIEW ARTICLE

What are the aims of the implementation of e-solutions in healthcare? Review of the relevant practical studies

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Abstract

The eHealth solutions are an effect of applying new technologies (ICT) in health care. The phenomenon is commonly described as transformation of the healthcare system as its influence on management and organization of care is both wide and deep. This review concentrate on aims of practical research along with an attempt to present useful stratification. The result of the study reveals that it is usually more than one goal of most of reviewed research. This lead to conclusion that the very early stage of research on eHealth should be based on picking its aims and relationship between them.

Keywords: aim • mHealth • eHealth • study design • healthcare value

Citation

Jędrzejczyk TW, Zarzeczna-Baran M. What are the aims of the implementation of e-solutions in healthcare? Review of the literature. Eur J Transl Clin Med. 2019;2(1):78-84.
DOI: 10.31373/ejtcm/104720

Introduction

The development of medical science has been always related to the progress of other technological and scientific discoveries. Computer sciences, telecommunication and electronic inventions were developed parallel to new medical procedures. EHealth (defined as medicine supported by electronic processes and communication tools), mobile health (mhealth, supported by mobile technology), ICT (information

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No external funds.

Available online: www.ejtcm.gumed.edu.pl

and communication technology) and telemedicine technologies are not merely new fashionable concepts but the tools which are increasingly used in healthcare since the late 1970s. These technologies goes along with the way how medical services are provided. Practitioners and researchers pointed some benefits which are related to technological development in their field. These improvements require a great expenses as well as scientific involvement by healthcare providers and governmental agencies. Public spending spurs new technology which nonetheless requires an evaluation of the outcomes. As long as 30 years ago the European Commission started to support eHealth initiatives, providing around 500 million euro for approximately 400 projects between 1988 and 2003 [1]. Investment in eHealth is still increasing, with 197.5 million euro are to be spent in years 2018-2020 [2].

Although the above-described are only complementary to the basic healthcare functions (prevention, diagnosis, treatment and rehabilitation), the impact of eHealth on the organization of medical services is substantial. The exact assessment of the impact of a given eHealth solution on actual improvement requires deployment of adequate methodological tools. The complete research process on eHealth and telemedicine consists of five stages: concept development, service design, pre-implementation, implementation and post-implementation analysis [3]. The contemporary knowledge upon eHealth use needs systematic evaluation.

Material and methods

Google Scholar database was Boolean searched with various of keywords combination: “eHealth”, “research”, “effectiveness”, "healthcare", “study” “patient”, “value”, “project”, “data”, “disease”. E-scholar database was chosen due to its unique characteristic, including multidisciplinary and widely open for diversified editors, direct open access of the full-text of numerous articles. Studies published since 2015 were screened. The top most five cited articles were selected from every search for further evaluation (synthesis), taking into account how long given article was accessible. The inclusion criteria were as follows: clinical trials, cases reports and reviews of original trials. The extraction of the declared aim and methodological approach was performed than the process of aggregation into broader categories was performed. The complete review of articles was presented together with the specific application of given study.

Results

Following study search and selection, 28 articles were included in the review synthesis. The selection process revealed a broad spectrum of interest among eHealth of their authors. The aims of studies were identified, the results of review were presented according to the area of interest.

Out of 28 studies, 15 (53.6%) had 1 specific research aim, 8 (28.6%) had 2 aims and 5 (17.8%) were designed to find out 3 aims. The most popular research question was healthcare effectiveness. The definition of “healthcare” was defined very broadly in the reviewed articles, including health promotion, education, diagnosis, treatment and rehabilitation. Secondly, articles focused on patients’ perception and attitude towards new technological solutions in healthcare delivery. The 3rd and 4th goals of the analyzed articles were professional perceptions of eHealth solutions and improving their quality through better data collection and aggregation. On the other hand, only 1 paper focused on the safety of the patients’ care. Along with the identification of the aims of the studies we paid attention on what kind of research was undertaken to present it in the given article. The most common was qualitative study while randomised controlled trials were rare way to study the phenomenon of eHealth.

Discussion

Health education and promotion

The development of internet continues to bring an exponential increase in information including health promotion. Furthermore, it is challenging for the reader to verify the quality and accuracy of the available data. Therefore, granting public access to seemingly valuable information is not an efficient way to increase awareness of health risks or to support individuals in making healthy choices. Thus it is not surprising that one of the principal aims of eHealth studies is assessing the actual response to the delivered information [6, 13].

Early diagnosis - interviews

Web questionnaires are a useful and time-saving tool to gather information from patients and thus support and shorten the actual face-to-face interview. This can be applied on the level of provider and improve communication with patients before their scheduled appointments. Moreover, online surveys could target larger group of individuals. A few studies aimed at improving the quality of such tools [19].

Table 1. Podpis do tabeli

Reference	Aims (according to the authors)	Cited/months available online	Comments/type of study
[4]	Influence of professionals' attitude for better patient self-management	29/25	qualitative study
[5]	Effectiveness and quality (completeness od data) of eHealth tool vs standardised, opportunistic recruitment	19/36	cluster randomised controlled trial
[6]	Adherence of life-style intervention along with economic evaluation	5/13	randomized controlled pilot trial
[7]	Adherence of life-style intervention	8/24	randomized controlled trial
[8]	Safety of eHealth based intervention	5/20	meta-review
[9]	Assess effect of eHealth patient-managed system	1/12	randomized controlled trial
[10]	Addressing challenges experience by people with morbidity	2/14	qualitative study
[11]	Patients' empowerments implication on MDs	8/9	qualitative
[12]	Dimensions of patient engagement	74/34	review
[13]	Interactions between patient and health care provider based on internet information, and ethical care.	34/40	quality study
[14]	Electronic health record - access influence of expectancy of performance	36/37	questionnaire
[15]	Reason of dropouts of eHealth intervention	14/17	qualitative
[16]	Compliance level using eHealth solution for MI patients	23/26	randomised controlled trial

[17]	Efficacy of crowdfunding for eHealth project	4/0	case study
[18]	Evaluate critical incidents while using e-health solution (patients' portal)	15/29	qualitative
[19]	Evaluation of the quality of web-communication vs direct meeting	5/11	qualitative, experimental
[20]	Cost-utility and reach of eHealth solution	6/21	research protocol
[21]	Collecting data decrease patients with undiagnosed FH	39/22	research protocol
[22]	Assess of possible empowering patients thanks to eHealth solution	13/38	multicentre and multitask research
[23]	Validate eHEALS questionnaire as a measure of eHealth literacy skills	16/12	comparative study
[24]	Validate the smartphone application as the diagnostic tool - way of assuring good data quality	2/24	qualitative study
[25]	Effectiveness of eHealth intervention - impact on behaviour	3/21	comparative cross--sectional study
[26]	Examine the experience of using eHealth solution for gathering patient - generated data in outpatient clinics	15/23	qualitative study
[27]	Comparison of patients' expectation of eHealth solution for disease control and self-management	21/28	quality - focus group
[28]	Assess impact of eHealth solution on lifestyle intervention	2/5	randomized control trial
[29]	Efficacy of eHealth technology used in managing rare disease	2/3	systematic review
[30]	The role of eHealth solution in patients' empowerment process	2/5	review
[31]	eHealth tool effectively used for integrating healthcare	1/17	planned / controlled trial

Patient - provider communication process

In many countries patient-oriented care became the new goal of the both public and private healthcare providers. Specifically, one of the most important values to patients is a so-called "good communication" with health care providers. We know intuitively that this element of patient-oriented care could be possibly facilitated by ICT tools. The question whether implementing such ICT solutions is reasonable. It was proved that this aim is nearly impossible to achieve without an appropriate engagement of healthcare providers [30].

Treatment and rehabilitation

Organising home-based care can be difficult due to logistics, possible costs and obstacles to quality supervision at the same time. In this field, telemedicine became an accepted solution which facilitates the healthcare process while keeping cost under control. There are numerous examples of successful implementations of such projects [6, 9, 16, 20]. Parallel to their achievements, there is a constant need to evaluate the new solutions. Technologies can replace some of the problems related to the so-called "human factor" and improve work [5, 24]. However Black et al. indicated that there is gap between the postulated benefits and the expectations of ICT solutions. The future eHealth technologies need evaluation [32]. Of the numerous studies published so far, only two systematic reviews on eHealth and two on mHealth were validated by Cochrane Groups [33-35]. One of the emerging challenges is the quality of introducing and management of health information system, which requires basic technological knowledge from both the managerial and non-managerial staff. Moreover, systematic evaluation and interpersonal abilities engage more personnel.

Conslusions

Though eHealth obviously involves technology, the attitude of healthcare providers, payers, regulators and representatives of healthcare professionals looking to implement such solutions should be holistic and not merely technologically and economically focused [36]. Economic evaluation of any eHealth technology is still evolving and therefore needs standardization. While the evaluation of pharmaceutical substance can be easily based on randomized control trial, in the field of eHealth it is more complex and thus demanding [37].

The most important part of research assessing the implementation of an e-solution in any healthcare organisation is to clearly define the aim [38].

Summarizing, we currently face the rapid increase of the reports on eHealth solutions. The process of planning further projects in this field should be preceded by a careful revision of current achievements. It would be more beneficial if future studies address real problems of healthcare.

This review revealed that most of studies about eHealth attempted to assess more than one problem.

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EUROPEAN JOURNAL OF TRANSLATIONAL
AND CLINICAL MEDICINE 2019;2(1):85-95

BIORESOURCE PAPERS

Biobank Łódź® – population based biobank at the University of Łódź, Poland

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Abstract

Background: Biobank Laboratory of the University of Łódź is a unit in the organizational structure of the Department of Molecular Biophysics at the Faculty of Biology and Environmental Protection. It was established in 2014 as one of the results of the TESTOPLEK project. One of the main goals of the unit is to collect and share biological material of human origin and related clinical and survey data. Moreover, Biobank Laboratory conducts work in the field of genetics and molecular biology on human biological material. Biobank Laboratory gathers over 40.000 samples such as DNA, FFPE, saliva, together with their data. Data about its material is available for researchers in directories e.g. BBMRI-ERIC Directory 4.0. Since 2014, the unit belongs to the national Consortium BBMRI.pl, and since 2017 it executes a project entitled Research Infrastructure for Biobanks and Biomolecular Resources BBMRI-ERIC, co-creating the Polish Network of Biobanks. Biobank Laboratory is focused on cooperation with domestic and foreign scientific institutions and medical units, as well as entities from the local, business and public sector.

Keywords: biobank • population biobank • sample quality control • BBMRI-ERIC • data

Citation

Dobrowolska S, Michalska-Madej J, Słomka M, Sobalska-Kwapis M, Strapagiel D. Biobank Łódź – population based biobank at the University of Łódź, Poland. Eur J Transl Clin Med. 2019;2(1):85-95.
DOI: 10.31373/ejtcm/109495

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Funding source: This work was supported by the Polish Ministry of Science and Higher Education—Project DIR/WK/2017/01.

Available online: www.ejtcm.gumed.edu.pl

Introduction

Biobank name

Biobank Laboratory, Department of Molecular Biophysics, Faculty of Biology and Environmental Protection, University of Łódź [1].

Biobank ID

Biobanking directory: BBMRI-ERIC Directory 4.0 [2].
ID: PL_BLUL

Biobank contact

- Address: 14/16 Józefa Pilarskiego Street,
- 90-231 Łódź, Poland
- URL: www.biobank.uni.lodz.pl
- e-mail: biobank@uni.lodz.pl
- Phone number: +48 42 665 57 02
- Corresponding person: Dr. Dominik Strapagiel,
- dominik.strapagiel@biol.uni.lodz.pl

Biobank history

Biobank Laboratory of the University of Łódź is a unit in the organizational structure of the Department of Molecular Biophysics at the Faculty of Biology and Environmental Protection, established by the Resolution of the Dean of the Faculty of Biology and Environmental Protection of 25/03/2014.

Biobank Laboratory was created as one of the results of the TESTOPLEK project – full name *Role of multidrug resistance proteins in pharmacokinetics and toxicology – in vitro tests in pharmaceutical and clinical practice* (2008-2014) [3-5].

Over 10.000 individuals nationwide were canvassed to create a retrospective POPULOUS collection (POPUlation – LOdz UniverSity Biobank). The next step was the acquisition of collections of clinical samples, including breast cancer patients (BREAST), patients with pancreatic cancer (PANC), as well as a representative collection of samples from the school-age population from the city of Łódź (PUPILS).

Since 2014, the unit belongs to the national Consortium BBMRI.pl, and since 2017 it executes a project entitled Research Infrastructure for Biobanks and Biomolecular Resources BBMRI-ERIC (Biobanking and BioMolecular Resource Research Infrastructure - European Research Infrastructure Consortium), co-creating the Polish Network of Biobanks [1, 6-7].

Biobank legal status

Public; a part of Department of Molecular Biophysics, Faculty of Biology and Environmental Protection, University of Łódź [8-9].

Current biobanking activity

Longitudinal study; collecting; processing; storage.

Main biobank aim

One of the main goals of the unit is to collect and share biological material of human origin and related clinical and survey data. Moreover, Biobank Laboratory conducts work in the field of genetics and molecular biology on human biological material.

Biobank membership

- BBMRI.pl (Biobanking and BioMolecular resources Research Infrastructure – Consortium) [6],
- BCNet (Biobank and Cohort Building Network) [10],
- ESBB (European and Middle Eastern Society for Biopreservation and Biobanking) [11],
- co-creating the Polish Network of Biobanks [6].

Certification

Biobank Laboratory has European certificates from IBBL (Integrated Biobank of Luxemburg) [12] in the fields of:

- DNA Quantification and Purity,
- RNA Quantification and Purity,
- DNA Extraction from Whole Blood,
- RNA Extraction from Whole Blood,
- Microbial DNA Extraction from Saliva,
- CSF Aliquoting [13].

Some employees of the unit have certification as lead auditors in the field of information security and quality management granted by leading international and national centres [14].

International system standards

In the near future Biobank Laboratory plans to implement international standards related to management systems, such as PN-EN ISO 9001:2015 Quality management systems – Requirements and PN-EN ISO/IEC 27001:2017 Information security management system – Requirements.

Scientific and research projects

TESTOPLEK: *Role of multidrug resistance proteins in pharmacokinetics and toxicology – in vitro tests in pharmaceutical and clinical practice* – POIG grant 01.01.02-10-005/08 TESTOPLEK from the European Regional Development Fund (2008-2014).

BBMRI: *Research Infrastructure for Biobanks and Biomolecular Resources BBMRI-ERIC* – Polish Ministry of Science and Higher Education no. DIR/WK/2017/01 (2017-2021).

POPC: *Digital sharing of biomolecular and descriptive resources of Biobank and Department of Anthropology, University of Łódź – characteristics of populations living in present-day Poland through the ages. Information platform e-Czlowiek.pl* – Polish Ministry of Science and Higher Education no. DIR/WK/2017/01 (Operational Programme Digital Poland for 2014-2020).

Let`s BioIT: *Let's Bio-IT development of professional, bioinformatic, language and entrepreneurial skills of students of the Faculty of Biology and Environmental Protection, University of Łódź* – Project no. POWR.03.01.00-00-K410 / 16-00 (2017-2019).

POLPHARMA: *The study of the importance of epigenetic processes in the pathogenesis of mastocytosis to find new therapeutic options* founded by Polpharma Scientific Foundation (2018-2021).

Organization structure of biobank

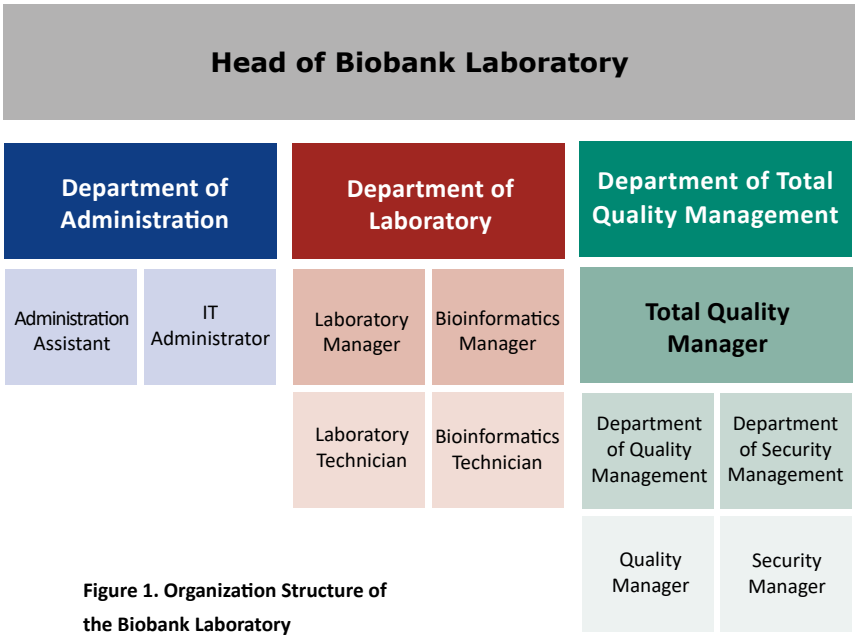

Figure 1. Organization Structure of the Biobank Laboratory

Percentage share of the type of biobanked material Collections

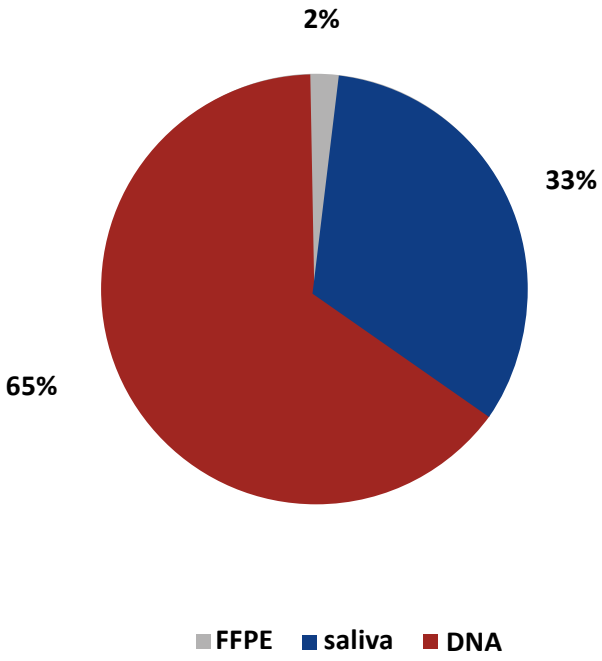

Figure 2. Percentage share of the type of biobanked material

Collection and sample

Biobank category	*Material type*
Population based	Saliva; DNA; FFPE

POPULOUS – saliva; DNA; the collection was created for the project TESTOPLEK; retrospective; anonymized; POPULOUS_BLUL [3-4, 15-23].

BREAST – FFPE; DNA; the collection was created for the project TESTOPLEK; retrospective; anonymized; BREAST_CANCER_COLLECTION_BLUL.

PANC – DNA; saliva; the collection was created for the project TESTOPLEK; retrospective; anonymized; PANCREATIC_CANCER_COLLECTION_BLUL.

PUPILS – saliva; the collection was created within a grant from the Mayor of the City of Łódź (559/VI/11) and project TESTOPLEK; prospective; pseudoanonymized; ANTHROPOLOGICAL_STUDY_PUPILS_BLUL [5, 24-28].

BREAST IBUL – DNA; retrospective; anonymized [29-31].

Geographical origin of samples from the collection

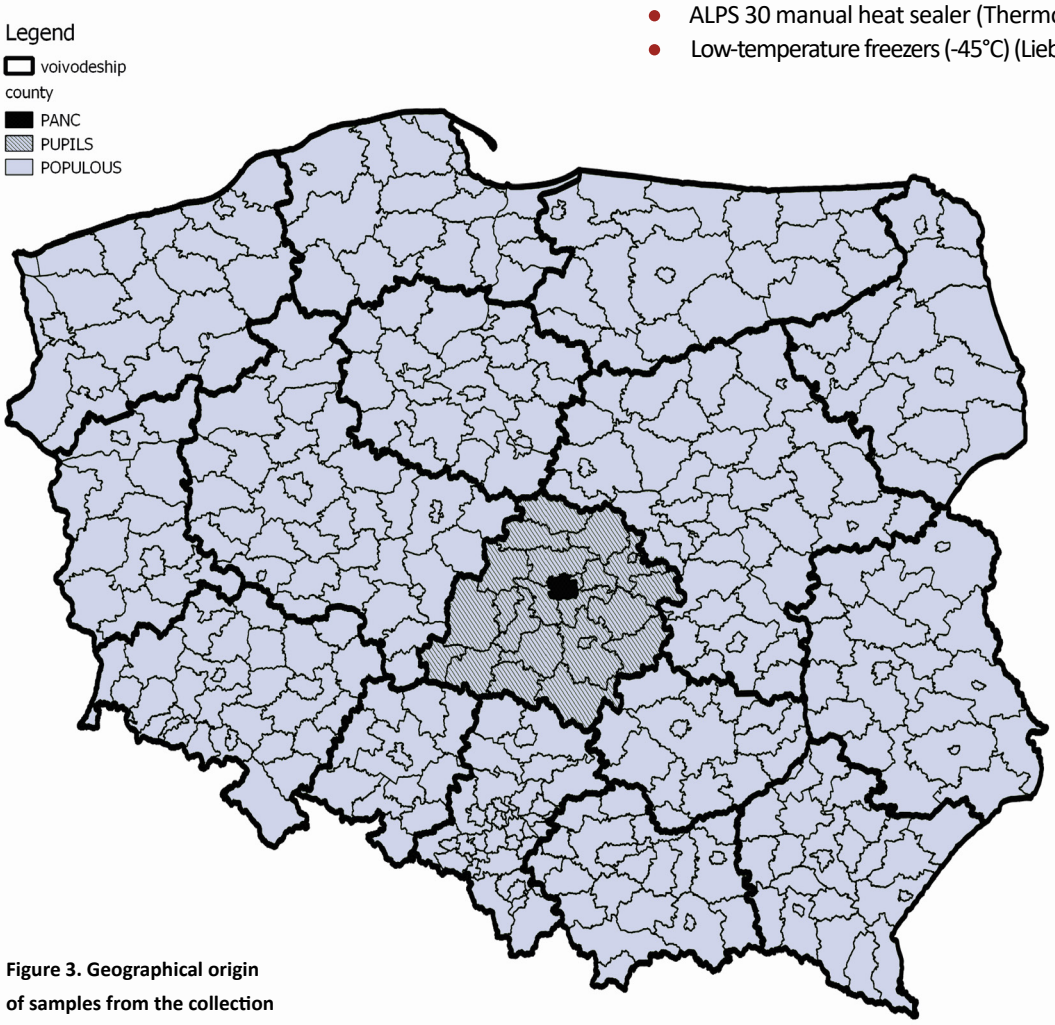

Figure 3. Geographical origin of samples from the collection

BREAST and BREAST IBUL collection have no specific information about geographical origin of donors [32-33].

Characteristics of samples in collection

Description of material collected in collections, according to Table 1.

Storage conditions

-50°C; -27°C; room temperature (18-25°C)

Biobank Equipment

- NextSeq500 (Illumina Inc.),
- MinION (Oxford NanoPore Technologies),
- Liquid Handling Robot Janus (Perkin Elmer),
- Liquid Handling Robot MagNa Pure LC 2.0 (Roche),
- Automatic arm for transferring microplates (LabMind),
- TECAN Workstation (Illumina Inc.),
- Scanner iScan (Illumina Inc.),
- ALPS 30 manual heat sealer (Thermo Scientific),
- Low-temperature freezers (-45°C) (Liebherr Medline),
- Low-temperature freezers (-86°C) (New Brunswick Scientific),
- UV3 HEPA PCR Workstations (UVP),
- Laminar Workstations Maxi Safe 2020 (Thermo Scientific),
- Chamber for long storage of DNA in room temperature (BioMatrica),
- ThermalCycler C1000 (BioRad),
- CFX Real-Time PCR Thermal Cycler C1001 (BioRad),
- Automatic sample sorter XL20 (BioMicroLab),
- LightScanner (IDAHO Technology)
- Milli-Q (Millipore),
- DNA microplates decapper (Polgen),
- Single TEC control (INHECO),
- Hybex microsample incubators (SciGene),
- Hybridization ovens (Illumina Inc.),
- Qubit 2.0 Fluorometer 2.0 (Invitrogen),

- FastGene Mini centrifuge (NipponGenetics Europe),
- Centrifuge MPW-352R (MPW),
- Pippin Prep (Sage Science).

Donors

POPULOUS – no information about diagnosis, available donor declarations about their diseases (Tumors of soft tissues; Symptomatic atherosclerosis of coronary vessels not treated with stents; Diabetes; Hypothyroidism; Psoriasis; Lung cancer; LDL-C hypercholesterolemia above 130 mg / l; Multiple sclerosis; Symptomatic atherosclerosis of coronary vessels treated with stents; Hyperplasia of the prostate gland; Malignant Hematoma and Non-Hodgkin's Lymphoma; Head and neck region cancer; Breast cancer; Allergy; Myasthenia gravis; Male genital cancers; Cancer of the urinary tract; Osteoporosis; Gastrointestinal neoplasms; Tumors of female genital organs; Leukemia; Thyroid cancer; Tuberculosis, including multi-drug resistant tuberculosis and other mycobacteriosis; Condition after myocardial infarction; Rheumatic diseases; Epilepsy; Parkinson's disease and syndrome; Alzheimer's disease; Asthma, Chronic obstructive pulmonary disease, eosinophilic bronchitis; Ulcerative colitis and Crohn's disease; Atherosclerosis; Condition after transplantation of a vascularized organ or bone marrow; Peptic ulcer disease – Helicobacter pylori infection detected and treated; Melanomas and skin cancers; Glaucoma); male and female; 18-90 ages.

BREAST – diagnosis: breast cancer / Malignant neoplasm of breast (C50-C50); female; available medical records, information about diagnosis and treatment.

PANC – diagnosis: pancreatic cancer / Malignant neoplasm of pancreas (C25); available medical records, information about diagnosis.

PUPILS – lack of information about diagnosis, available donor declarations about their diseases; male and female; ages 6-16.

BREAST IBUL - diagnosis: breast cancer / Malignant neoplasm of breast (C50-C50); female; available medical records, information about diagnosis.

Directories

- BBMRI-ERIC Directory 4.0 – information about collection [2],
- BioFace – information about biobank's samples,
- e-Człowiek platform – information about anthropological collection,
- metaBiobank – information about collection [34].

Communication protocol

- BioScoop 1.0 – communication protocol used for BioFace and e-Człowiek platform [35],
- Miabis 2.0 – communication protocol used for BBMRI-ERIC Directory 4.0 [36].

Principles of sharing samples and materials

In order to gain access to biobanked samples, please contact the Biobank Laboratory Manager and present the context of the use of samples in research. The request is subsequently evaluated in terms of formal, legal and ethical compliance with the rules of Biobank Laboratory and Polish law. Following a positive decision, the material is anonymized and transmitted to researcher. Each transfer of samples is contingent upon signing an MTA (Material Transfer Agreement) in which the nature of the access is determined. The researcher may use the samples only for the purposes specified in the MTA.

Samples management system

For the needs of the TESTOPLEK project, Biobank Laboratory created its own system of sample management (SMS). At present, Biobank Laboratory as a member of Polish Biobank Network uses BBMS (BioBank Management System) to manage samples. The SMS system is still used as a form of verifying the correctness of data migration to BBMS [37].

Quality control of samples

Quality control of biobanking samples is based on internal quality procedures (SOP – Standard Operational Procedure). At every step, samples are evaluated by quality tests. Each internal method is verified and validated by qualified Biobank staff. Quality procedures are based on generally accepted standards and the experience and knowledge of employees.

In addition, selected internal biobank procedures are evaluated by external quality tests – Proficiency Testing Program performed by IBBL (Integrated BioBank of Luxembourg) to confirm their quality. The pro-quality testing program is endorsed by ISBER (International Society for Biological and Environmental Repositories) [12, 38].

Collection and samples databases

Format of shared data

Format of genetics/raw sequencing shared data:

- .fastq
- .ped
- .map
- .bam

Format of medical shared data:

- .csv

Format of image shared data:

- .jpg
- .tiff
- .S3Dm

External repository of data

- e-Człowiek.pl platform,
- EGA – European Genome-phenome Archive [39],
- SRA – Sequence Read Archive (available on NCBI) [40],
- WGS – Whole genome sequencing (available on NCBI) [40],
- BioProject (available on NCBI) [40],
- BioSample (available on NCBI) [40].

Principles of sharing data

All data stored by the Biobank Laboratories are subject to strict access control. Access to data can be obtained on the basis of individually negotiated licensing agreements – DTA (Data Transfer Agreement). The DTA determines the detailed scope of data access and processing capabilities. Depending on the scope of the DTA, additional contracts may be required. Shared data should be kept confidential and should only be used for tasks related to the implementation of the agreement. In order to obtain access to data, please contact the Manager of the Biobank Laboratory specifying the use of the data.

Ways of sharing data

Encoded external disc, FTP servers, commercial data sharing services.

Data management system

BBMS – BioBank Management System [37].

Ethics

Institutional Review Board

Any activity that uses biological material collected by the Biobank Laboratory is controlled by the Institutional Review Board of the University of Łódź (IRB). The Head of Biobank Lab is an active member and participates in the legislative work of the IRB.

In order to use the material each researcher should submit an appropriate application to the IRB. IRB gives its opinion on the proposal in terms of its scientific validity and feasibility, and respecting the rights of participants in the research experiment.

After receiving a positive opinion from the IRB, the researcher may start recruiting donors to create a new collection or start research on the already created collection.

Regulations

Every activity of the Biobank Laboratory in the area of biobanking conforms to the following regulations:

- Declaration of Helsinki: ethical principles for medical research involving human subjects [41],
- Data Protection Code, Polish Data Protection Authority [42],
- Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation) [43],
- Resolution of Institutional Review Board of the University of Łódź.

Other information

Form of contact for those interested in cooperation with biobank

Information about collections, samples and data can be found in the catalogues described above. In order to get direct access to resources, please use the data below.

- e-mail: biobank@uni.lodz.pl,
- Phone number: +48 42 665 57 02,
- Corresponding person: Dr. Dominik Strapagiel, dominik.strapagiel@biol.uni.lodz.pl

External Biobank activity

Biobank Laboratory has a modern and very well-equipped laboratory, adapted to perform research in the field of genetics and molecular biology.

The unit cooperates with the public and private sector, offering services such as:

- DNA, RNA tests (DNA and RNA isolation from various biological materials),
- study of genetic variation using classical methods of molecular biology such as: PCR, real-time PCR, Sanger sequencing [18], high-resolution melting of PCR products (HRM) [3-4, 17, 21, 26, 44-45], Taq-Man probes,
- measurements of selected parameters of the tested material (fluorometric testing of the DNA concentration),
- separation of nucleic acids using horizontal, vertical, capillary electrophoresis,
- genomic DNA testing using microarrays (e.g. GWAS) [15-16, 20, 22-23],
- next generation sequencing (Illumina Platform, Nanopore Sequencing),
- gene expression testing (RNA-seq, microarray and qPCR) [46-51],
- epigenetic analysis (Chip-Seq, DNA methylation analysis, methylation RNA),
- microorganism genome analysis (de novo sequencing, variant calling) [44, 52-57],
- eukaryotes whole genome and targeting sequencing,
- aDNA analysis [58-59],
- human genome analysis (variant calling, NGS Target Enrichment, whole exome sequencing),
- amplicon sequencing,
- metagenomics and metabarcoding,
- bioinformatics analysis.

Biobank Laboratory applies an open data policy that allows broad access to data for interested researchers.

Biobank Laboratory conducts teaching and educational activities, engaging in numerous social projects for University of Łódź students and local community in Łódź.

Patent

- Method for identification of pathogenic fungi species contained in a sample taken from a patient – number P.408 734 [60],
- Method for determination of gender – number P. 406 569 [61]
- Method for determination of gender – number P. 423 420 [62],
- Method and a set for the detection of genetic predisposition to having a certain hair colour – number P. 403 360 [63].

Vision and plans for future

In the near future, Biobank Laboratory plans to expand its headquarters and acquire more highest class infrastructure for biobanking. Moreover, the unit plans to implement international standards related to management systems such as PN-EN ISO 9001:2015 Quality management systems – Requirements and PN-EN ISO/IEC 27001:2017 Information security management system – Requirements.

Major barrier

The main challenge for our unit is to recruit donors of biological material. Biobank Laboratory as a university unit is not a medical facility, creating difficulties in contact with potential donors. In addition, considering the population-based character of the biobank, Polish legislation lacks regulations regulating this area of biobanking.

Acknowledgments

The authors would like to thank Łukasz Pułaski for language editing, Jakub Lach and Justyna Jarczak for methodical supporting which improved the manuscript. This work was supported by Polish Ministry of Science and Higher Education - Project no. DIR/WK/2017/01

Conflict of interests

The authors declare no conflict of interest.

Table 1. Basic information about material stored in biobank

Collection name	Directory + ID number	Material type	Number of samples	Storage containers	Processing	Storage medium	Storage conditions	Corresponding person
POPULOUS	BBMRI-ERIC Directory 4.0, POPULOUS _BLUL	saliva	12000	Original Tubes from ORAGEN Kit DNAGenotek	N/A	Original preservative medium from ORAGEN Kit DNAGenotek	RT (18-25°C)	dominik.strapagiel@biol.uni.lodz.pl
POPULOUS	BBMRI-ERIC Directory 4.0, POPULOUS _BLUL	DNA	24000	MICRONIC	Automatic (MagnaPure LC 2.0, Roche); Etanol/ isopropanol precipitation	Elution Buffer (Roche), H_2O, TE buffer	-50 or -27°C	dominik.strapagiel@biol.uni.lodz.pl
BREAST	BBMRI-ERIC Directory 4.0, BREAST_CANCER_COLLECTION_BLUL	DNA	800	MICRONIC	Xylen extraction; Isolation Automatic (MagnaPure LC 2.0, Roche);	H_2O, TE buffer	-50 or -27°C	dominik.strapagiel@biol.uni.lodz.pl
BREAST	BBMRI-ERIC Directory 4.0, BREAST _CANCER _COLLECTION_BLUL	FFPE	800	Eppendorf tube	N/A	N/A	RT (18-25°C)	dominik.strapagiel@biol.uni.lodz.pl
PANC	BBMRI-ERIC Directory 4.0, PANCREATIC_ CANCER_ COLLECTION_BLUL	DNA	90	MICRONIC	Etanol /isopropanol precipitation	H_2O, TE buffer	-50 or -27°C	dominik.strapagiel@biol.uni.lodz.pl
PANC	BBMRI-ERIC Directory 4.0, PANCREATIC_ CANCER_COLLECTION_BLUL	Saliva	90	Original Tubes from ORAGEN Kit DNAGenotek	N/A	Original preservative medium from ORAGEN Kit DNAGenotek	RT (18-25°C)	dominik.strapagiel@biol.uni.lodz.pl
PUPILS	BBMRI-ERIC Directory 4.0, ANTHROPOLOGICAL_STUDY_ PUPILS_BLUL	DNA	961	MICRONIC	Etanol /isopropanol precipitation	H_2O	-50°C	aneta.sitek@biol.uni.lodz.pl
PUPILS	BBMRI-ERIC Directory 4.0, ANTHROPOLOGICAL_STUDY_ PUPILS_BLUL	Saliva	961	Original Tubes from ORAGEN Kit DNAGenotek	N/A	Original preservative medium from ORAGEN Kit DNAGenotek	RT (18-25°C)	aneta.sitek@biol.uni.lodz.pl
BREAST IBUL	N/A	DNA	250	MICRONIC	N/A	H_2O, TE buffer	-50 or -27°C	katarzyna.wozniak@biol.uni.lodz.pl

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