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PRACA POGLĄDOWA
REVIEW

Epidemiological and clinical aspects of *Polyomaviridae* infections – a literature review

Epidemiologiczne oraz kliniczne aspekty zakażeń wirusami z rodziny *Polyomaviridae* – przegląd literatury

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ABSTRACT

Polyomaviridae (PyV) are small, non-enveloped viruses leading after infection to mainly asymptomatic or oligosymptomatic disorders among different vertebrates. Currently 14 PyV are known to affect human health. This literature review aims to summarise accessible knowledge from both epidemiological and clinical studies conducted on healthy and PyV infected human populations, with a focus on studies containing transplantation and oncology issues. The search strategy involved screening four databases and finally 25 studies were selected for this article. The majority of the studies focused on the influence of BKPyV and JCPyV infections on renal graft recipients. Some research also described the prevalence of MCPyV and future oncological treatment. The results revealed that various types of patient fluids and tissues may be useful in PyV detection. Moreover, heterogeneity in available evidence on each PyV is observed. The studies implied possible future directions for PyV studies, including new biomarkers, the examination of risk factors or comparison of the course of the disease and treatment results in various age groups of patients.

KEYWORDS

viruses, *Polyomaviridae*, infections, transplantation, kidneys, heart, oncology, epidemiology

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STRESZCZENIE

Do rodziny poliomawirusów (*Polyomaviridae* – PyV) należą małe, bezotoczkowe wirusy, które po wniknięciu powodują głównie bezobjawowe lub skąpoobjawowe zakażenia u różnych kręgowców. Dotychczas odkryto 14 PyV, które wpływają na zdrowie człowieka. Celem niniejszego przeglądu literatury było podsumowanie dostępnej wiedzy z badań epidemiologicznych i klinicznych, przeprowadzonych na zdrowych i zakażonych PyV populacjach ludzkich, ze szczególnym uwzględnieniem problemów występujących w transplantologii i w onkologii. Strategia wyszukiwania obejmowała przegląd czterech wyszukiwarek baz danych; ostatecznie do niniejszego artykułu zostało wybranych 25 badań. Większość z nich dotyczyła wpływu zakażeń wirusami BK i JC na pacjentów z przeszczepionymi nerkami. Część opisywała także występowanie wirusa MC i przyszłe leczenie onkologiczne. Wyniki wskazały, że w diagnostyce zakażeń PyV mogą być użyteczne różnorodne płyny i tkanki pacjenta. Co więcej, można było zaobserwować, że badania nad poszczególnymi PyV różniły się jakością dowodu. Wnioski z przytoczonych artykułów nakreśliły przyszłe kierunki badań nad zakażeniami PyV: nowe biomarkery, wpływ czynników ryzyka czy też porównanie przebiegu choroby i wyników leczenia w różnych grupach wiekowych pacjentów.

SŁOWA KLUCZOWE

wirusy, poliomawirusy, zakażenia, transplantacja, nerki, serce, onkologia, epidemiologia

INTRODUCTION

The viruses assigned to the *Polyomaviridae* (PyV) family are said to induce some asymptomatic or oligosymptomatic infections in various vertebrates [1]. What is more, the name of the family indicates the potential oncogenicity of some of them, especially in the case of specifically generated conditions [2]. They have been known since mid-XX century, with murine PyV discovered in leukemic mice organs and fluids by Gross [3] and described later by Eddy and Stewart [4]. However, the ongoing development of both laboratory techniques and technology results in further diagnostics and continuous distinction of more than 100 PyV viruses. Nowadays, only 14 PyV affect humans, and their genomes are found mainly in body fluids [1,5,6]. Some PyV are named in accordance with the abbreviations either of the names of first patients from whom they were isolated or the disease they may develop [1,5,7].

PyV belong to small (40–45 nm), non-enveloped double-stranded DNA viruses [7]. Their icosahedral capsids contain genomes with approximately 5300 base pairs that code structural viral proteins and small, large and sometimes middle tumor antigens [7,8]. Those tumor antigens, varying in size and exact origin, contribute to the mechanisms of viral replication and oncogenic transformation [8]. Furthermore, some studies showed the ability of PyV to transmit and then infect different species, including humans [9]. BK polyomavirus (BKPyV), JC polyomavirus (JCPyV), Merkel cell polyomavirus (MCPyV) or the Trichodysplasia spinulosa-associated polyomavirus (TSPyV) are said to develop severe disorders and became the objects of high impact research [5]. What is more, PyV infections are often diagnosed in an advanced stage of the disease, after a decreased function of the organ is observed [10].

This article aims to describe the current state of knowledge about the epidemiology and medical aspects of some PyV human infections, with renal disorders, transplantation issues and potential oncogenicity emphasized.

METHODOLOGY

The literature review was conducted in February 2024, employing a comprehensive search strategy across four databases: PubMed, Embase, Web of Science and the initial 100 results from Google Scholar. The search parameters were predicated upon three key terms: “Polyomaviridae”, “Polyomavirus”, “Epidemiology”. Notably, the strategy utilized in PubMed is delineated in Figure 1.

((Polyomaviridae[Title/Abstract]) OR (Polyomavirus[Title/Abstract])) AND (Epidemiology[Title/Abstract])

Fig. 1. Advanced search strategy in PubMed database.

The research inquiry was formulated following the PICO framework (patient or problem, intervention or exposure, comparison or control, outcomes), and the methodological approach adhered to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) standards.

A total of 2835 scientific articles were initially identified, from which 667 papers were retained following the elimination of duplicates, materials incompatible with the study focus, book chapters, reviews and case reports. Subsequently, a meticulous examination of the retrieved articles was conducted, considering language accessibility criteria (excluding articles not in English or lacking full-text access). After the selection process, two independent reviewers carefully selected 25 of the most relevant studies based on their perceived value, which are outlined in the following manuscript.

RESULTS

It is said that BKPyV causes nephropathy in immunocompromised patients, which may lead to the complete failure of kidney transplantation [11]. JCPyV is known to be the reason for multifocal leukoencephalopathy and MCPyV may cause Merkel cell carcinoma (MCC) [12,13]. Nevertheless, in the beginning PyV infections are often asymptomatic, with patients receiving positive results from specific blood or urine tests [14].

PyV among healthy or patients with diseases not associated with PyV infection

Egli et al. [12] conducted a study on healthy blood donors, aiming to analyse the prevalence of BKPyV and JCPyV in a population of donors (n = 400). The presence of BKPyV and JCPyV was detected in 82.0% and 58.0% of the donors respectively. Moreover, the percentage of people infected by JCPyV decreased along with the decreased age of the donors, but that dependence was reversed in a BKPyV test. The results from this study also contained the donors' urine test results. It occurred that 19.0% of the donors had JCPyV in their urine and 5.0% of them had BKPyV in that fluid. Only in the donors who had JCPyV did the elevated levels in blood correlate with the ones in urine. The findings from the study conducted in 2020 by Dehcheshmeh et al. [14] on an asymptomatic population (164 collected samples, 60% females) stated that 5.2% females and 8.8% males tested positive for the JCPyV 3A genotype. Furthermore, BKPyV genotype III was found respectively in 11.5% and 14.7% of them.

In addition, there are also studies focusing on the presence of MCPyV in patients diagnosed with skin cancers. Mertz et al. [15] described the prevalence of MCPyV in 21.3% of potentially healthy patients, 40.9% cases of basal cell carcinoma (BCC) and in 28.0% of squamous cell carcinoma (SCC). It also occurred that the majority of those patients (in total 210 people in the study group) did not display mutations or immunological features distinctive for MCC.

Gossai et al. [16] conducted a study on PyV prevalence among 113 patients diagnosed with SCC and a group of 229 healthy people. The results showed that SCC prevalence was correlated with a prior presence of JCPyV. The majority of the patients with diagnosed BKPyV (98.8%) or JCPyV (87.1%) before the confirmation of SCC remained seropositive. Moreover, there were steady rates of BK infections in different age groups of healthy people, but the JC rates were increased in older men (> 65 years old).

Furthermore, Mogha et al. [17] described the influence of solar simulated radiation (SSR) on the transcription rate in MCPyV positive female patients. Twenty skin samples of healthy patients were examined and then doses of 2 and 4 J/cm^2 SSR were used. It occurred that 2 patients were infected. It was then confirmed that the activity of the small T promotor was correlated with SSR.

The studies described below are placed in non-chronological order, only depending on the various issues of PyV infections raised.

PyV among renal graft recipients

The first prospective study on the presence of BKPyV, JCPyV and cytomegalovirus (CMV) in 48 graft recipients was conducted by Gardner et al. [18] in 1984. It was reported that 95.8% of the recipients received kidneys from deceased donors. Approximately 50.0% of the recipients were diagnosed with PyV infection during the first 3 months of the follow-up. Concurrent CMV infection was reported in 93.0% of the ill individuals. The majority of the patients presented with an asymptomatic infection, whereas only 6.3% reported ureteric stenosis, vomiting and malaise in the case of the presence of BKPyV, and effusion with pericarditis in the case of JCPyV infection. During completion of the follow-up, it was determined that PyV were diagnosed finally in 65.0% of the recipients and CMV in 62.5% of the whole sample. Moreover, decreased kidney function was diagnosed in 26.0% of the ill. Nonetheless, 81.0% of the recipients did not report any kidney issues after the transplantation.

Furthermore, López et al. [10] described the 1-year prevalence of BKPyV and JCPyV in urine samples from 76 graft recipients. The results indicated that 96.0% of the patients survived this period. In general, it was assessed that PyV viremia was found in 9.2% of them and PyV viruria in 40.7% of the recipients. What is more, only 3.9% of them were diagnosed with nephropathy after the follow-up period. The analysis of the glomerular filtration rate (GFR) among the recipients with and without developed nephropathy showed that GFR was significantly lower in the patients with the decreased renal function, however, no kidney was lost due to that disorder. Completion of the administered immunosuppression therapy led to diminished rates of recipients with maintained PyV viruria (32.0% of the previously affected patients) and viremia (42.8% of them).

Mengelle et al. [19] described the presence of JCPyV DNA in the blood samples of 103 patients after kidney transplantation. The recipients with reported JCPyV infection (6.8% of all) were administered antithymocyte globulins or anti-CD25 monoclonal Ig before transplantation. After the surgery, they were treated with combinations of various treatment agents: mycophenolate mofetil, ciclosporin A, steroids, tacrolimus, or belatacept. The median time of JCPyV detection was approximately 139 days after the

operation. The patients with JCPyV did not present with any specific symptoms. In addition, there was not no recipient with reported nephropathy. Nevertheless, there were single cases of concurrent BKPyV--associated nephropathy with decoy cell shedding.

The outcomes from the study on 214 living pairs of donors and recipients by Schwarz et al. [11] showed that BKPyV infection found in the recipients before the transplantation was a risk factor for future nephropathy (10.3% of recipients). What is more, 40.0% of the recipients presented with BKPyV viruria after the surgery and approximately 72.0% of the patients from that group were diagnosed with viremia. The allograft function was assessed as worse in comparison with the PyV-negative kidney transplant recipients. Additional research in the field of BKPyV subtypes showed that in BKPyV-positive pairs, the viral transmission was compatible in 86.0% of them.

The study of Dolci et al. [20] focusing on the presence of PyV in allograft biopsies and in the urine examined during subsequent follow-up visits in 58 pairs of donors and recipients showed that viruria was detected in 50.0% of the donors and 70.7% of the recipients at the beginning. Both JCPyV and BKPyV genomes were found, with BK revealed in 37.9% of the recipients and 5.2% of the donors and JC in 43.1% and 44.8%, respectively. Some recipients had their kidney transplanted from a PyV-positive donor. Moreover, the median times from transplantation to a urine positive test result varied significantly – 1 day in the case of JCPyV and 171 days for BKPyV. No statistical correlation was found between PyV infection and allograft function, but the patients with diagnosed JCPyV viruria presented with a smaller probability of BKPyV viruria after transplantation.

What is more, Chan et al. [21] carried out a study among 139 renal transplant recipients on BKPyV infection in the biopsy or the blood sample. It occurred that BKPyV viremia was diagnosed in 20.9% of the recipients and the presence of BKPyV in the biopsy was found in 5.0% of the patients. High blood variables connected with the patients' concurrent diseases, like hyperlipidemia (levels of triglycerides, low-density lipoprotein fraction of cholesterol and total cholesterol rate) and diabetes mellitus (HbA1c rate or results of fasting blood sugar test) were assessed as the risk factors for PyV infection. However, the courses of BKPyV infections among the patients varied and the levels of PyV elimination were also different. Viral elimination was observed in the majority (75.0%) of patients treated with intravenous immunoglobulins (Ig) in the first 3 months from the beginning of the treatment.

Costa et al. [22] reported that an analysis of 23 renal transplant biopsies with diagnosed BKPyV showed that lower GFR and older age may influence graft loss. The majority of patients (95.7%) had their kidney transplanted from deceased donors. The recipients were administered calcineurin inhibitors (95.7% tacrolimus) together with corticosteroids; additionally, 70.0% of them were also given an antimetabolite drug. One year after a reduction or the discontinuance of such therapies, decreased functioning of the transplanted kidney was reported in 48.0% of the patients. The PyV nephropathy and concurrent delayed graft function resulted in graft loss in 39.1% of the recipients.

Furthermore, Huang et al. [23] described BKPyV replication and nephropathy among 90 patients after renal transplantation. It was assessed that 22.2% of the recipients developed BKPyV viremia and 45.6% developed viruria. Nephropathy was diagnosed in 5.6% of the patients. The administration of cyclosporine A resulted in a lower probability of later BKPyV diagnosis (28.9%) in comparison with tacrolimus (57.7%). Moreover, BKPyV viremia was not reported in 95.0% of the ill after the completion of therapy and this state did not affect the grafts. Higher predictive values were achieved due to implementation of the decoy cell count as a biomarker of PyV nephropathy (57.1%) and viremia (85.7%).

Soleymanian et al. [24] conducted a prospective study focusing on the prevalence and stage of BKPyV infection in 32 recipients during a 1-year period after transplantation. Grafts from living donors represented 75.0% of all the transplantations. Despite the fact that viremia was discovered in 25.0% of the patients, none of them developed nephropathy. The 4-month follow-up showed that there were 62.5% recipients with viremia who also had BKPyV positive blood results. Nonetheless, after 1 year there was only 1 patient (12.5%) with such a diagnosis. The study population was treated with cyclosporine A (84.4%), prednisolone and mycophenolate mofetil.

In addition, Kamminga et al. [25] collected blood serum samples from 620 recipients and corresponding 279 donors to check the presence of JCPyV, MCPyV, TSPyV and human polyomavirus 9 (HPyV9) before, 6 months and a year after the surgery. The levels of corresponding immunoglobulins G (IgG) were measured. The study determined that the IgG levels were elevated in 14.8% of the recipients for JCPyV, 10.6% of the patients for TSPyV, 8.1% of the recipients for HPyV9 and 7.1% of them for MCPyV. In addition, the seroconversion rates in the transplant recipients were assessed as 6.5% for JCPyV and HPyV9, 2.3% for MCPyV and 1.3% for TSPyV. No seroconversion was observed in the group of donors. However, it occurred that the results were statistically significant only for JCPyV and HPyV9.

The prospective study conducted by Bialasiewicz et al. [26] on urine, blood samples and respiratory swabs from 167 kidney recipients aimed to determine the scope of human PyV that might be detected. The patients were examined before the transplantation, on

day 4, 1, 3 and 6 months after the surgery, and reported BKPyV viremia episodes. BKPyV and JCPyV were reported respectively in 29.3% and 14.4% of the recipients. It occurred that HPyV9, human polyomavirus 12 (HPyV12), nor MWPyV were found in any patient. Other than the most common BKPyV and JCPyV, human PyV were observed in respiratory swab samples. The majority of PyV detections were found during transplantation or 1 month after the operation. Moreover, all the KIPyV samples displayed in total the greatest viral load. In the case of concurrent BKPyV/JCPyV and any other human PyV infection, it was assessed that the rates of those rarer PyV were significantly lower.

In contrast to that, there was also a comparative study by Castro et al. [27] on the usage of gingival fluid to detect BKPyV and JCPyV among 12 renal transplant recipients, 14 patients with chronic kidney disease (CKD) and 20 healthy humans. It occurred that JCPyV was discovered in 51.7% of the patients after kidney transplantation, 14.0% of the CKD patients and 45.0% the potentially healthy men. The presence of PyV in that fluid was observed in 91.7%, 100.0% and 80.0%, respectively. Moreover, PyV were detected in gingival fluid even in the case of their absence in the blood or urine samples, depending probably on the stage of the infection.

As the diagnostics of PyV is developing, Fang et al. [28] prepared a dynamic prediction model for BKPyV reactivation after kidney transplantation in adult patients. That model was based on the retrospective analysis of 312 patients. The variables: acute rejection of the transplanted organ, neutrophil rate in the blood, urinary protein and leukocyte levels, older age of the recipient, the treatment scheme: basiliximab and cyclophosphamide; elevated body mass index and estimated glomerular filtration rate are said to impact BKPyV reactivation.

PyV among heart graft recipients

There was a prospective study on BKPyV incidence and disorders conducted among 12 children with transplanted hearts by Ducharme-Smith et al. [29]. Ten recipients completed the follow-up period. The blood serum and urine of the patients were examined prior to the transplantation, during week 1 and 3, 6, 9, 12, and 15 months after the transplantation. BKPyV viremia was reported in 10.0% of children and viruria was present in 20.0% of them. Nephropathy was not diagnosed in any of the recipients, however, kidney function was assessed as worse in the patients with a confirmed BKPyV diagnosis.

MCPyV infection resulting in MCC

To begin with, MCPyV was discovered in MCC skin biopsy specimens and then estimated by Feng et al. [30] to be present in even 80.0% (8 patients out of 10) of the MCC lesions. The examination was based on both skin fragments from 25 healthy patients and other tissues from 59 different people. MCPyV prevalence was found in 16.0% and 8.0% of those samples, respectively.

Nghiem et al. [31] described the results of the treatment scheme of one or more doses of Pembrolizumab 2 mg per kilogram (kg) body weight every 3 weeks in 26 patients. It was determined that 65.4% of them had MCPyV induced MCC. A satisfactory level of treatment response was achieved in 62.5% of the seropositive people and in 44.4% of the seronegative ones. Multispectral fluorescent immunohisto-chemistry, screening for MCPyV-specific CD8 T cell peptide-MHC tetramer and small T-antigen oncoprotein antibody titers were measured and performed to examine the current status of MCPyV in the patients.

In addition, Nghiem et al. [32] also presented a similar study on 50 patients. In that study group 64.0% of the MCC patients were seropositive. The overall response rate was assessed as 56.0%, however, in the seropositive subgroup it was ascertained to be 59.0%.

Kaufman et al. [33] conducted a study on 88 patients treated with an Avelumab scheme of 10 mg per kg body weight every 2 weeks. The study group consisted of 46 patients with MCPyV-positive MCC; 31 of the ill with MCPyV-negative MCC and an additional 11 of them with an unknown MCPyV status. The objective response rate was assessed as 33.0%. No statistical correlation between the response rate and the prevalence of MCPyV was found.

Furthermore, the study from D'Angelo et al. [34] of 116 patients also treated with Avelumab showed a 39.7% objective response rate during an average follow-up of 21.2 months. There were 60.3% seropositive patients enrolled in the study. The durable and objective response rates were higher for the MCPyV-negative patients than for the MCPyV--positive patients (respectively 39.1% and 27.1%, 48.6% and 34.3%).

What is more, Topalian et al. [35] prepared a study on resectable MCC treatment among 39 patients that received Nivolumab 240 mg intravenously on days 1 and 15. The surgery was planned for the 29th day of the treatment. MCPyV was found in 62.9% of the examined specimens. It occurred that 54.5% of the patients were then examined and displayed a tumor reduction of $\geq 30.0\%$. The achieved response rate had no correlation with the presence of MCPyV.

Summary of studies

Table I displays all the studies which results were described in this literature review. The papers are listed in chronological order.

Table I. Summary of articles described in this literature review

Virus (PyV family)	Year	Authors	Type of study	Study group size	Types of samples examined
BK, JC	1984	Gardner et al. [18]	prospective	n = 48	blood serum urine
MC	2008	Feng et al. [30]	comparative	n = 94	skin biopsy specimen
BK, JC	2008	López et al. [10]	prospective	n = 76	blood serum urine
BK, JC	2009	Egli et al. [12]	prospective	n = 400	blood serum urine
BK	2010	Huang et al. [23]	prospective	n = 90	blood serum urine
MC	2010	Mogha et al. [17]	controlled clinical trial	n = 20	skin biopsy specimen
JC	2011	Mengelle et al. [19]	prospective	n = 103	blood serum
MC	2013	Mertz et al. [15]	clinical trial	n = 210	skin biopsy specimen
BK	2014	Soleymanian et al. [24]	prospective	n = 32	blood serum
BK, JC, MC, WU, KI, HPyV6, HPyV7, TS, STL	2016	Bialasiewicz et al. [26]	prospective	n = 167	blood serum urine respiratory swabs
BK, JC	2016	Gossai et al. [16]	randomized clinical trial	n = 342	skin biopsy specimen blood serum
MC	2016	Nghiem et al. [31]	clinical trial	n = 25	skin biopsy specimen blood serum
BK	2016	Schwarz et al. [11]	prospective	n = 428	blood serum urine
BK, JC	2017	Castro et al. [27]	case-control	n = 12	gingival fluid saliva mouthwash blood serum urine
BK	2017	Costa et al. [22]	retrospective	n = 23	renal graft biopsy specimen blood serum
BK	2017	Ducharme-Smith et al. [29]	prospective	n = 12 at beginning, then n = 10	blood serum urine
MC	2018	Kaufman et al. [33]	clinical trial	n = 88	blood serum
MC	2019	Nghiem et al. [32]	clinical trial	n = 50	skin biopsy specimen blood serum
BK	2020	Chan et al. [21]	longitudinal cohort observational	n = 139	renal graft biopsy specimen blood serum
BK, JC	2020	Dehcheshmeh et al. [14]	comparative	n = 164	urine
MC	2020	Topalian et al. [35]	clinical trial	n = 39	skin biopsy specimen blood serum
MC	2021	D'Angelo et al. [34]	clinical trial	n = 116	skin biopsy specimen
JC, MC, TS, HPyV9	2021	Kamminga et al. [25]	cohort	n = 899	blood serum
BK	2022	Fang et al. [28]	retrospective	n = 312	not applicable (prediction model)
BK, JC	2024	Dolci et al. [20]	prospective	n = 116	renal graft biopsy specimen urine

CONCLUSIONS

To conclude, the number of studies on the immunology and clinical management of human PyV infection has increased in recent years. The majority of studies focus on BKPyV, JCPyV and MCPyV. There is a need to examine the role of biomarkers and the usage of other fluid samples than blood serum or urine to detect future PyV disorders. Furthermore, the issue of the potential risk factors for symptomatic PyV illness should be developed. The outcomes showed the demand for rapid screening tests including PyV before transplantations, even for the most vulnerable patients. More comparative studies on PyV infections among children or among all age groups should be conducted. The results also revealed a percentage of healthy people with a concurrent presence of PyV. Some studies on the prevalence of PyV in other illnesses, especially in oncology could be carried out to examine potential correlations with the treatment efficacy.

The main limitations of this literature review include the number of screened databases, heterogeneity in the quantity and quality of studies focusing on each PyV, and the various types of patient samples used in each study. Some clinical studies did not include control groups or fully described methodology to allow us to better evaluate the potential risk of bias.

Conflict of interest

None declared.

Author's contribution

Study design – Ł. Sędek, Z. Czuba, A. Kozub
Data collection – A. Kozub, A. Nasiek
Manuscript preparation – A. Kozub, A. Nasiek
Literature research – A. Kozub, A. Nasiek
Final approval of the version to be published – Ł. Sędek, Z. Czuba

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