Arch Virol
DOI 10.1007/s00705-015-2343-0

BRIEF REVIEW

Merkel cell polyomavirus infection in childhood: current advances and perspectives

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Received: 29 October 2014 / Accepted: 17 January 2015

Abstract Merkel cell polyomavirus (MCPyV) is a newly discovered human small, non-enveloped, double-stranded DNA virus, which was classified into the *Polyomaviridae* family. MCPyV is acquired in early childhood through close contact involving respiratory tract secretions and causes a widespread, previously unrecognised, asymptomatic infection in both immunocompetent children and adults. To date, several researchers have established that MCPyV is the potential causative agent of Merkel cell carcinoma, a relatively rare but life-threatening skin cancer of neuroendocrine origin. In our review, we present current data on the presence of MCPyV DNA in children and address the possible role that the respiratory tract plays in the route of viral transmission. Future studies are required to fully elucidate the potential implications of MCPyV infection in children.

Abbreviations

ALTO	Alternative tumor antigen open reading frame
BKPyV	BK polyomavirus
HIV	Human immunodeficiency virus
HPyV	Human polyomavirus
JCPyV	JC polyomavirus
KI	Karolinska Institute
LT	Large tumor antigen
MCC	Merkel cell carcinoma
MCPyV	Merkel cell polyomavirus
MPyV	Mouse polyomavirus
NCRR	Non-coding regulatory region
NSCLC	Non-small-cell lung carcinoma
PCR	Polymerase chain reaction
sT	Small tumor antigen
STLPyV	Saint Louis polyomavirus
SV40	Simian vacuolating virus
TSPyV	Trichodysplasia spinulosa polyomavirus
VP1-3	Viral protein 1-3
WU	Washington University

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Introduction

Polyomaviruses, classified into the *Polyomaviridae* family, are small (40–45 nm), non-enveloped viruses with icosahedral symmetry and a circular double-stranded DNA genome [37]. Polyomaviruses can infect a variety of vertebrates, including humans, and can cause malignant tumors when inoculated into heterologous hosts [32]. Mouse polyomavirus (MPyV), identified in 1953 as a tumor-causing agent in mice, was the first polyomavirus identified, followed by simian vacuolating virus (SV40), which was isolated from rhesus monkey kidney cells that were used in 1960 for the preparation of the vaccine against poliovirus, the causative agent of poliomyelitis [37].

In humans, the unique characteristics of human polyomaviruses (HPyVs), such as their ability to establish latent infection, their potential for reactivation during immunosuppression, and their well-documented oncogenic properties render them of considerable importance for global public health [8, 10, 37]. The discovery of the first two HPyVs, BK polyomavirus (BKPyV) and JC polyomavirus (JCPyV), took place in 1971 [37]. The first of these was isolated from a urine sample from a renal transplant

Published online: 10 February 2015

patient, and the other was isolated from the brain tissue of a patient with progressive multifocal leukoencephalopathy; both were named after the patients' initials. Both viruses are oncogenic when inoculated into newborn rodents; however, to date, no role of BKPyV and JCPyV in human carcinogenesis has been reported [8, 37].

Over the past decade, advances in molecular methods, including sequencing technologies, have led to an unexpected increase in the number of HPyVs identified [32]. In 2007, two new HPyVs, KI (Karolinska Institute) and WU (Washington University) – named after the initials of the institutes, where they were first described – were identified independently from nasopharyngeal aspirates from children with acute respiratory tract infections. In 2008, the fifth HPyV, named Merkel cell polyomavirus (MCPyV), was isolated from a skin tumor sample from a patient with Merkel cell carcinoma (MCC). Since the discovery of MCPyV and its causative association with MCC, six new HPyVs have been identified that have not yet been associated with any disease [32, 37]. These include HPyV 6, HPyV 7, HPyV 9, HPyV 10 and HPyV 12 [11, 32], as well as Saint Louis polyomavirus (STLPyV), which was identified by Lim et al. [27] in a stool sample from a healthy child in Malawi. In 2010, trichodysplasia spinulosa-associated polyomavirus (TSPyV) was described and associated with trichodysplasia spinulosa, a rare proliferative skin disorder only observed in immunocompromised patients [34]. Among all of the newly discovered HPyVs, to date, MCPyV has recently attracted the most attention by several research teams, worldwide [2, 13, 14, 21].

The virology of MCPyV

MCPyV is a small, non-enveloped, double-stranded DNA virus, which belongs to the HPyV group [37]. Its 55–60 nm viral capsid has the typical icosahedral symmetry found in all HPyVs [8]. First described in January 2008, the prototype MCPyV (Fig. 1) has a 5,387-base-pair genome and contains an early region, a late region and a non-coding regulatory region (NCRR) [8, 28]. The early region encodes characteristic polyomavirus genes, including the large tumor (LT) antigen, the small T (sT) antigen, and the 57kT antigen, and can also contain an alternative T antigen open reading frame (ALTO). Viral protein 1 (VP1), viral protein VP2 (VP2) and viral protein 3 (VP3) are late proteins, encoded by the late region, that are required for capsid formation and viral replication [8, 12]. NCRR contains the early and late transcriptional promoters, as well as the viral origin of replication, which can be mapped to 71 bp of contiguous sequence recognized by the LT antigen [8].

The MCPyV T antigen, which is expressed in human tumors, shares similar characteristics with the T antigens of

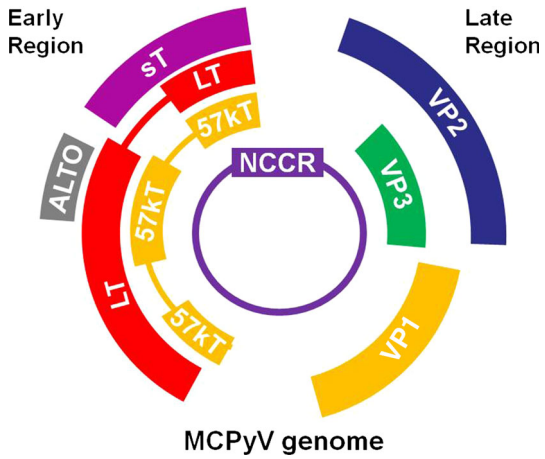

Fig. 1 Schematic diagram of the genomic organization of the MCPyV prototype. Non-coding control region (NCCR), early region: large T (LT) antigen, small T (sT) antigen, 57kT (57kT) antigen, alternative T antigen open reading frame (ALTO). Late Region: capsid viral protein 1 (VP1), capsid viral protein 2 (VP2), capsid viral protein 3 (VP3)

other polyomaviruses, which are known oncoproteins [31]. The T antigen is a spliced gene and, dependent on the splicing pattern, produces multiple different proteins. LT and sT antigen proteins both have the ability to transform healthy cells into cancer cells through the targeting of tumor-suppressor proteins, such as retinoblastoma protein. Several researchers have investigated the genomic diversity of MCPyV based on the nucleotide sequences of LT and VP1 gene sequences [7, 15, 28]. Construction of LT- and VP1-gene-based phylogenetic trees has allowed the identification of five main clades, which are phylogenetically supported and correspond to the different continents where they occur: a. North America/Europe (Caucasian), b. Africa, c. Asia, d. Oceania, and e. South America [15, 28]. The larger clades are the Caucasian group, including sequences from North America and Europe, as well as sequences from French Caucasians and individuals of African origin, and the African group, including not only sequences isolated from central Africa (Cameroon) but also strains from Noir-Marron individuals who were living in French Guiana but whose ancestors originated from West Africa around two centuries ago [28].

MCPyV and human carcinogenesis

Although HMPyVs are typically non-oncogenic [37], several researchers have documented the presence of MCPyV in MCC and have suspected its causative role in human carcinogenesis [2, 13, 14, 21]. Interestingly, the genome of MCPyV has been detected in approximately 80 % of MCC cases [11]. MCC is a relatively rare, highly aggressive,

human skin cancer of neuroendocrine origin, but its worldwide incidence has increased over the past twenty years from 500 to 1,500 cases per year [2, 14, 21]. It occurs mostly in individuals between 60 and 80 years of age, and more frequently than expected in individuals who are immunosuppressed, including organ transplant recipients and those who have been infected with human immunodeficiency virus (HIV). In the majority of MCC cases, MCPyV is integrated into the host genome in a monoclonal fashion, and the viral T antigen has truncating mutations that render the T antigen unable to initiate the DNA replication required to propagate the virus [21, 37].

A research issue that has been addressed recently is whether MCPyV plays a role in the pathogenesis of lung cancer [3, 12, 16, 18, 20, 22, 26]. Interestingly, the presence of integrated MCPyV DNA has been demonstrated in non-small-cell lung carcinoma (NSCLC) specimens. Although the prevalence of virus was low in these cases, several tumor-specific molecular characteristics support the possibility that MCPyV is partly associated with the pathogenesis of NSCLC in a subset of patients [16]. Interestingly, analysis of gene expression in MCPyV-positive patients with NSCLC has revealed the deregulated expression of *BRAF* and *BCL-2* genes, which contributes to the pathogenesis of NSCLC [22, 26]. However, further research is required before an etiopathogenic role of MCPyV in lung carcinogenesis can be proven [3].

MCPyV epidemiology in adulthood

The presence of MCPyV in the upper respiratory tract has been suggested to be a general characteristic of HPyV infections of adults [1, 6, 18, 23]. Recent molecular and serological data have suggested that MCPyV infection is common in the general immunocompetent population [9, 24, 33]. In a study by Goh et al. [18], MCPyV DNA was detected in 27 of 635 (4.25 %) nasopharyngeal aspirate samples by real-time polymerase chain reaction (PCR). In a study by Bialasiewicz et al. [6], MCPyV DNA was detected in 7 of 526 (1.3 %) respiratory tract samples from patients in Australia with upper or lower respiratory tract symptoms. MCPyV has also been detected in tonsils, nasal swabs and nasopharyngeal aspirates in adults [23]. In a study by Kantola et al. [23] of 1,390 samples from immunocompetent and immunocompromised patients, MCPyV DNA was detected in 3.5 % of tonsillar tissues, 2.1 % of nasopharyngeal aspirates, and 1.9 % of nasal swabs. Recently, in a study by Babakir-Mina et al. [4], MCPyV DNA was detected in 15 out of 87 (17.24 %) lower respiratory tract samples from adult patients admitted to hospital.

Recent seroepidemiological studies of healthy adults have documented MCPyV seroprevalence in the general population, ranging widely from 61 to 96.2 % [30, 36]. Recently, Nicol et al. [30] documented that MCPyV seroprevalence in adults aged 80 years and older can reach 91.1 %. In adulthood, a significant increase with age in both genders has been documented [30, 36]. Serological evidence also suggests that non-sexual horizontal spread of MCPyV can occur among family members [36]. In cases with detected IgM and IgG against MCPyV, the frequency of viremia is extremely low, indicating that serodiagnostics should be the strategy of choice for the diagnosis of primary infections with MCPyV [9]. MCPyV seroconversion is always asymptomatic [9].

MCPyV in childhood

Serology of MCPyV in childhood

Recent serological data (Table 1) have suggested that MCPyV infection is common in childhood [9, 10, 17, 24, 28, 30]. Interestingly, as shown in a serological study by Kean et al. [24] using ELISA and employing recombinant VP1 capsid proteins, the MCPyV seroprevalence early in life is similar to that in the adult population. However, other researchers have found that MCPyV seroprevalence in healthy adult blood donors increases gradually in children aged 15 years or younger and in persons older than 50 years [9, 10, 24, 29, 30, 33, 35]. In a study by Chen et al. [9], the seroprevalence of MCPyV IgG was 9 % at 1 to 4 years and increased to 35 % at 4 to 13 years, with a 33 % seroconversion rate from age 5 to 8 years. A similar age-related increase in seroconversion rates was reported by Kean et al. [24]. In a study by Viscidi et al. [35], who detected capsid antibodies against MCPyV, seroprevalence was 45 % in children under 10 years of age, increased to 60 % in the next decade of life, and peaked at 81 % in those 60 to 69 years of age. In a study by Nicol et al. [30], MCPyV seroprevalence increased with age from 41.7 % in children aged 1 to 4 years to 87.6 % in those aged 15 to 19 years.

Recent seroepidemiological data suggest that primary infection with MCPyV mostly occurs during early childhood, after the disappearance of specific maternal antibodies against MCPyV [10, 29]. Although the seroprevalence of maternal antibodies is high during infancy, antibodies are absent in children who had a viral infection during infancy, raising the possibility that maternal immunity may protect infants from infection by these viruses. [10, 29]. In a study by Martel-Jantin et al. [29], MCPyV seroprevalence was estimated to reach 70 % from birth until the age of 4 months. Interestingly, this seroprevalence is very similar to that observed in women of child-bearing age. Maternal antibodies against MCPyV

Table 1 Epidemiology of MCPyV infection in childhood

Year	References	Contribution
2008	Kean et al. [24]	MCPyV seroprevalence of 23 % among individuals under the age of 21 years
		Age-related increase in MCPyV seroprevalence
2009	Tolstov et al. [33]	MCPyV seroprevalence of 43 % among children aged 2–5 years
		No evidence of vertical MCPyV transmission among infants
		Age-related increase in MCPyV seroprevalence in childhood
2009	Goh et al. [18]	MCPyV prevalence in nasopharyngeal aspirates of 0.6 % among children aged 10 days-3 years
		Age-related increase in MCPyV DNA prevalence in nasopharyngeal aspirates
2009	Köksal et al. [25]	MCC in a child
2009	Kantola et al. [23]	Age-related increase in MCPyV DNA prevalence in tonsils in children
2009	Giraud et al. [17]	Absence of MCPyV in neuroblastomas and central nervous system tumors
2011	Viscidi et al. [35]	MCPyV seroprevalence of 45 % in children under the age of 10 years
		Age-related increase in MCPyV seroprevalence in childhood
2011	Abedi Kiasari et al. [1]	MCPyV prevalence in nasopharyngeal aspirates of 2 % among children aged 26 days-7 months
2011	Chen et al. [9]	MCPyV seroprevalence of 9 % in children aged 1–4 years
		Age-related increase in MCPyV seroprevalence in childhood
2012	Gustafsson et al. [19]	Absence of MCPyV in Guthrie cards of children who later developed acute lymphoblastic leukemia
2013	Martel-Jantin et al. [29]	MCPyV seroprevalence of 60–70 % in children aged 0–4 months reaching 0 % at 15–16 months of age
		Age-related increase in MCPyV seroprevalence in childhood
2013	Nicol et al. [30]	MCPyV seroprevalence of 41.7 % in children aged 1–4 years
		Age-related increase in MCPyV seroprevalence in childhood
2014	Chen et al. [10]	MCPyV seroprevalence of 3.4 % in children aged 0–4 years
		Age-related increase in MCPyV seroprevalence in childhood

progressively decrease with age, becoming undetectable by 15–16 months of age and then rapidly and steadily increasing at 17 months of age to reach about 60–80 % in children aged 4–5 years [29]. A significant sibling–sibling serologic correlation has been observed, particularly for siblings of similar age and between mothers and their children, indicating that MCPyV is acquired through close contact, possibly involving saliva and the skin [29]. No evidence of vertical transmission has been documented in infants [33]. Serological studies have found no evidence of a causative role of MCPyV in lower respiratory tract infections manifesting as acute wheezing in children [9].

MCPyV in the respiratory tract of children

MCPyV has been detected in nasopharyngeal aspirate samples collected from children, indicating the presence of MCPyV in the upper respiratory tract of children [1, 18]. The presence of MCyPV DNA has been demonstrated in 2 % of nasopharyngeal aspirate samples from immunocompetent children aged 26 days to 7 months [1]. MCPyV infection has been more commonly found in upper respiratory secretions of adults than in those of children [18]. Similarly, MCPyV DNA has been detected more frequently in the tonsils of adults than in those of children [23]. These data indicate that the presence of MCPyV DNA in respiratory samples from immunocompetent and immunocompromised patients is acquired gradually during childhood and that the respiratory tract plays a significant role in the route of MCPyV transmission in children [1].

MCPyV and childhood malignancies

MCC is extremely rare in children, and, to date, only a limited number of cases of children with MCC have been presented in the literature [25]. However, data from a larger number of MCC cases are required to clarify the molecular basis of this rare malignancy and to determine the potential role of MCPyV in childhood in the etiopathogenesis of MCC. In the future, further research will clarify whether MCPyV is present in childhood malignancies. To date, the presence of MCPyV has not been observed in childhood CNS tumors or neuroblastomas [17]. In a recent study, MCPyV was not detected in neonatal dried blood spots on Guthrie cards collected from 50 children who later developed acute lymphoblastic leukemia (ALL) [19].

Summary

MCC is a rare neuroendocrine tumor of the skin with highly aggressive behavior. It is usually fatal in cases of advanced disease [2, 5, 14, 21]. The high prevalence of MCPyV DNA in MCC suggests a potential role of MCPyV in human carcinogenesis [2, 13, 14, 21]. In the majority of cases, MCC is preceded by the integration of genomic sequences of MCPyV [21]. Future research is required to investigate the clinical significance of MCPyV infection in human carcinogenesis. Data from a larger number of MCC cases are required to clarify the molecular basis of this rare malignancy and to determine the potential role of MCPyV in the prognosis and treatment of patients. Current research has demonstrated that asymptomatic MCPyV infection is widespread in both immunocompetent children and adults, similar to other HPyV infections [9]. Serological studies have indicated that primary infection with MCPyV likely occurs during early childhood after the disappearance of specific maternal antibodies against MCPyV [9, 10, 24, 29]. The respiratory tract is involved as a unique reservoir of MCPyV in children, and seems to play a significant role in viral transmission in childhood. However, the clinical impact of the presence of MCPyV in children has yet to be clarified. Moreover, further research on MCPyV is required to investigate the significance of the presence of MCPyV in childhood malignancies, if any, as well as the role of this common infection of both adults and children in human carcinogenesis.

Conflict of interest The authors declare that they have no conflict of interest.

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