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Opportunistic Viral Infections After Kidney Transplantation: A Review

Asmaa B. Al-Obaidi[1] *PhD,* **Mervit B. Jasim** *MSc,* **Mustafa R. Hussein**[2] *FICMS,*
Haider S. Kadhim[1] *PhD,* **Manal A Habib**[3] *PhD*

[1]Dept. of Microbiology, College of Medicine, Al-Nahrain University, Baghdad, Iraq, [2]Baghdad Teaching Hospital, Baghdad, Iraq,
[3]Dept. of Pathology, College of Medicine, University of Baghdad, Baghdad, Iraq

Abstract

Opportunistic viral infections make an important threat to renal transplant recipients (RTRs), and with the use of more intense newly-developed immunosuppressive drugs; the risk of renal allograft loss due to reactivation of these viruses considerably increased. At the top priority of these viruses, human cytomegalovirus and other herpes viruses in addition to polyomavirus, reactivation of these viruses in these chronically immunosuppressed RTRs can lead to renal impairment and subsequently loss, unless early detected and properly treated.

Keywords kidney transplantation, viral infections

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List of abbreviations: ADV = Adenovirus, BKV = BK polyomavirus, BKVN = BK virus nephropathy, CMV = Cytomegalovirus, EBV = Epstein-Barr virus, HHV = Human herpes virus, JCV = JC polyomavirus, PTLD = Post-transplant lympho-proliferative disorder, RTR = Renal transplantation recipients VZV = Varicella-zoster virus

Introduction

Renal transplantation is the treatment of choice for patients with advanced kidney disease, even when compared with more sophisticated dialysis modalities [1,2]. Despite the significant advances in renal transplantation protocols, opportunistic infections especially viruses are still a potential cause of allograft failure, but also have been considered as an important cause of morbidity and mortality after kidney transplantation [3,4].

There are many different consequences of viral infections, which might include either direct effect on the graft and hematological dissemination to many other organs, or indirect effects on the patient and the graft [5]. Therefore, prevention, early detection, and prompt treatment of such infections are crucial in kidney transplant recipients [4].

Among all infectious complications, viruses are considered the most common agents because of their abundance, infectivity, and latency ability [4]. Herpes viruses like varicella-zoster virus (VZV), Epstein-Barr virus (EBV), and cytomegalovirus (CMV), hepatitis B virus, BK polyomavirus (BKV), and adenovirus are well-known etiologic agents of viral infections in kidney transplant patients worldwide because of their wide range of distribution [4].

As DNA viruses, they are able to reactivate after affected patients receive immunosuppressive agents. These DNA viruses can cause systemic diseases or allograft dysfunction, especially in the first six months after transplantation [4]. CMV and BKV are the most common causes of viral infection after

kidney transplantation. However, clinical presentations vary [4].

1- Cytomegalovirus (CMV)

CMV is a member of herpesviridae family virus, it is a β-Herpesvirus. It is the largest human herpesvirus, with a 150 to 200 nm diameter, and it has a lipoproteins envelope and 33 structural proteins, and the core, with a double-stranded DNA (64 nm) [6,7].

Generally, first infections usually occur in children, and the seroprevalence reaches more than 90% in the adults' population [8,9]. After first infection, the virus might be identified in the CD34+ myeloid progenitors and CD14+ monocytes, in addition to megakaryocytes, and dendritic cells [10,11].

During the situations of immune-suppression, like in solid organ transplants (SOT); CMV reactivation could take place, causing a wide spectrum of clinical manifestations in organ transplanted patients. Studies showed that CMV infection or reactivation is one of the primary infectious problems among renal transplantation, and it causes high incidence of both morbidity and mortality. Human CMV is regarded the most common viral infection in SOT, it is associated with clinically infectious diseases (e.g., fever, pneumonia, gastrointestinal ulcers, hepatitis, and retinitis) with acute or chronic renal allograft dysfunction. About 20-60% of all renal transplantation recipients (RTR) develop symptomatic CMV infection [10,12,13].

CMV infection could affect the kidney allograft either directly or indirectly. Direct effects of CMV might be CMV syndrome (e.g., fever, myalgia, fatigue, and leucopenia) or could be in the form of tissue invasive diseases (pneumonitis, duodenitis, gastritis, and colitis). While the indirect effects include acute or chronic renal allograft injuries, or allograft rejection, and causing other opportunistic infections mainly fungal [14].

Risk factors for the CMV reactivation are mainly low lymphocyte count [15,16], low complement activity or natural killer (NK) cells count [17,18], hypo-gammaglobulinemia mainly IgG type [17,19,20], seropositive donor and using lymphocyte depleting drugs [21,22]. The rate of occurrence of human CMV reactivation depends mainly on the donor/recipient serological (IgG) profile and it could reach up to 60% in RTR patients with D+/R- IgG CMV [23,24]. Also, the incidence could increase to 50% in RTR patient who receive T cell reduction therapy. Prevention of CMV infection after SOTs are prophylaxis anti-viral drugs [12,21,25].

Renal transplants with D+/R- CMV serostatus receive antiviral prophylaxis for more than 200 days [26]. The mainstay of treating tissue-invasive CMV diseases and CMV syndrome are intravenous ganciclovir or valganciclovir; these two drugs had the same efficacy on CMV-disease and also a similar long-term outcome [27].

2- Epstein- Barr virus (EBV)

Human EBV is a gamma-herpesvirus, reported with a sero-prevalence ranging from 70% to 90% in healthy subjects over the world [28-31]. Clinically, EBV infection presented among RTR in variable manifestations ranging from subclinical to uncomplicated infectious mononucleosis, pneumonitis, hepatitis, generalized lymphadenopathy, hepato-splenomegaly, central nervous system (CNS) disease, gastrointestinal (GIT) disease, and most importantly post-transplant lympho-proliferative disorder (PTLD) [32,33].

The prevalence of PTLD depends on the type of transplanted organ, however, RTR has the lowest. The risk factors for PTLD included type of the transplanted organ, EBV sero-mismatch, and the induction immune-suppressive therapy that is used mainly anti-thymocyte globulin (ATG), belatacept, and muromonab-CD3. The guidelines recommend screening for EBV DNA in blood in high-risk recipients for 1 year after transplantation because of the highest risk of reactivation within the first year [32-35].

Development of PTLD occurs in a biphasic onset, that means most of the EBV-positive RTRs develop PTLD in the first post-transplant

year, while EBV-negative RTRs develop PTLD 5-15 years post-transplant [36-38].

Intra-graft PTLD develops in the first 2 years post-transplant, while cerebral-PTLD develops between the 2nd and 7th year post-transplantation. However, the rate of GIT-PTLD is very low in the 1st 5 years and then increase in the 6th and 7th year post-transplantation [39].

Some of studies show that EBV DNAmia was detected in 19/57 (33%) of RTRs. About 50 and 51.7% of RTRs included in this study had either acute or chronic allograft impairment. In that study, RTRs with positive EBV DNAmia were commonly with high risk of having both acute and chronic renal impairment (P=0.0001), in addition, high serum creatinine levels in RTRs showed a significant risk to have EBV infection [40]. A study was conducted in Germany showed that EBV infection is an underestimated cause of renal allograft impairment and could be rejection of the renal allograft [41].

However, the exact risk cause for EBV infection to cause renal impairment is not well understood. Several explanations were speculated, EBV-induced cytotoxic T lymphocyte contains clones that are reactive to self-MHC-peptide which have strong allo-cross-reactivity against allo-MHC-peptides [8,42-44].

Other explanation is that EBV could counteract the immune-suppression of T lymphocytes in which induction of T cell immune response by EBV could be a limiting-step for immune-suppressive effects of drugs that were taken after renal transplantation [45].

In addition, the other EBV replicates in B-lymphocytes; which results in induction of B cells'-signaling pathway of producing immunoglobulins, which might result in an increased formation of heterophil antibodies. These heterophil antibodies could be another co-factor for tissues-targeting in the transplanted kidney, also complement activation might lead to renal glomeruli destruction [46].

3- Polyomaviruses

3.1 BK Polyomavirus (BKV)

BKV is a non- enveloped, ds DNA virus it is a member of Polyomaviridae family. It was first identified in 1971 in a RTR-patient who developed renal allograft impairment following kidney transplantation [47]. BKV infection after renal transplantation could cause BKV-associated nephropathy (BKVN), and graft-failure, hemorrhagic cystitis, ureteric stricture, and tubule-interstitial nephritis [48].

After the primary infection, BKV becomes latent in the uro-thelium and renal-tubular cells. After starting immune-suppression, the virus reactivates and starts replication, leading to BKV-viremia and finally affects the kidney allograft, causing BKVN. Rate of occurrence of BKVN is variable range from 1-10% [49-52].

Generally, there is a high seroprevalence rate of BK polyomavirus among healthy individuals, which reaches up to 91% [53]. A study of 400 blood donors, sero-prevalence rate reduced from 87% in young age-group (20 to 29 years) to 71% in the older age-group (50 to 59 years). BKV-shedding in urine was up to 7% in healthy subjects, however, BK-viremia was not found in blood of those subjects [54]. A study on 51 healthy subjects found BKV-shedding in urine was in about 16% of subjects, 28 of these healthy subjects were followed up for 6 months and the virus shedding in urine was very low in the majority of them [55]. Another study on 150 blood donors found that sero-prevalence of BKV was 82% [56].

Risk factors for the development of BKV infections in the renal transplant recipients could be classified into donor, recipient and transplantation related risk factors [47]. Studies showed that BKV viremia and BKVN occur most commonly in the 1st post-transplantation year, when immune-suppression is the most intense [57-59].

A study showed that the shedding of BKV in urine is significantly associated with BK viremia, BKVN, and allograft loss, RTRs who had positive urinary decoy cells were found to have BKV shedding in 56.3% of patients by urinary

polymerase chain reaction (PCR) testing. Also, BK viremia was positive in 93%, and BKVN was diagnosed by histopathological study in 48% of those patients. Most importantly, BK viremia higher than 104 copies/ml which is highly significantly-associated with a biopsy- proven BKVN (P<0.0001) [60].

BK polyomavirus infection presented with a gradual increase in serum creatinine levels with a tubule-interstitial nephritis that is mimicking rejection, which makes a therapeutic dilemma. The reduction of immune-suppression, which is needed to manage BKV infection is the opposite to the increase in immune-suppressive drugs which were needed to avoid rejection [51].

Schold et al. [61], investigated the incidence and risk factors for BK polyomavirus infection in RTRs. The significant and independent-risk factors were: a young age, donors over 65 years age, a male recipient, a female donor, higher HLA-mismatched, tacrolimus immune-suppression regimen, and induction by thymoglobulin.

In one study conducted on 99 RTR the results showed that BK viremia was in 12 out of 99 RTR (12.12%) with a viral load (VL) ranging from $1x10^2$ to $1x10^9$ copies/ml [62]. In a study the results revealed there was a significant correlation between creatinine values and BKV viral load (r=+0.576) (p=0.05) [62].

There is no significant association between the type of immune-suppressive regimen and BKV viremia (p=0.42). Many of studies found a highly significant correlation between decoy cells in the Pap-stained urine cytology smears and BK viremia one of these of studies conducted by Al-Obaidi et al., P value were (p=0.001) [63]. Reactivation of BKV could cause hemorrhagic cystitis, ureteric stenosis and bacterial super-infections [57-59]. Some of these studies found BK infection highly associated with co-infection of CMV, whereas other studied showed no significant association between these two viruses in RTRs [59,64-66].

Differences in the type of cellular immune response to BKV might play important role in the reduction of BKV replication. Positive BK viremia patients had lower CD4 count; and higher CD8 in the pre-transplant samples, as compared to the transplanted subjects who didn't develop BK viremia [67].

3.2 JC Polyomavirus (JCV)

JCV is member of the Polyomaviridae family, it is a non-enveloped virus with a double-stranded DNA genome [68]. JCV was first identified by Padgett et al. [69] in 1971 in brain of patient with the initials JC, who died because of progressive multifocal leuko-encephalopathy (PML), a progressive deadly demyelinating disease in the CNS.

Studies of JCV in kidney transplanted recipients were published after identifying the virus [70,71]. Infection by JCV was observed in RTRs as nephropathy or PML. Progressive Multifocal leuko-encephalopathy rarely occurs in kidney transplanted patients and it is mainly correlated with high levels of JC viral DNA in the cerebrospinal fluid (CSF) [72].

Kidney transplanted recipients had the highest risk of complication with polyomavirus nephropathy (PVAN) as compared to other SOT due to the development of allograft injury due to drug toxicity, cold ischemia, and HLA-mismatch, all these in addition to polyomaviruses activation [73,74]. Polyomavirus nephropathy with renal allograft dysfunction and loss has been significantly increasing since 1990s; so that, a pathological role of JCV should be considered [75,76].

Gardner et al. [77] performed prospective, serological study on JCV infection in 48 kidney transplant recipients, and showed that 54% of the subjects were sero-positive before transplantation, and in 23% of the sero-negative patients, JCV infection occurred in the first 3 months post-transplantation. Most surveys that measured JCV viremia in patients' samples, had reported wide range of JCV loads, from 2.0×10^3 to 1×10^7 copies/ml [40,78-83]. Most of studies showed that JC viral load was significantly increased in the RTRs compared to the healthy group, verifying the correlation

between patients' immune status and viral loads [84,85].

According to a study conducted on 71 RTRs Quantitative real time PCR gave positive JCV viruria in 31 out of 71 (43.7%) RTRs and 2 (10%) out of the 20 controls, (P=0.007) [84]. However, JC viremia in the RTRs seems to be very rare, and low as it is shown in some studies. The extent of tissue involvement by JCV is less than that in BKV nephropathy. However, some of studies suggested a role of JCV in renal allograft nephropathy among RTRs just like BKV [60,67,86-89].

Most of studies, documented a significant correlation between JCV and abnormal creatinine clearance, in one of these this study where a about 58% of those who had abnormal creatinine clearance also had positive JC viruria, which was significantly higher than those who had negative JC viruria. Most of studies found that the Decoy cell shedding was not significantly associated with JC viruria, unlike BKV which most of studies showed significant correlation with DC shedding. There are studies, showed that cyclosporine (CYC) is a risk factor for JCV reactivation. In once found 21RTRs out of 31 RTRs (67.7%) positive JC viruria were on CYC regimen [67,90-95].

4- Human herpesviruses-6, -7 and -8

Human herpesvirus-6 and -7 (HHV-6 and HHV-7) are well recognized pathogens in organ transplant recipients, they are homologous to CMV and in the same subfamily. Human herpesvirus-6 in RTR has been found to be associated with fever, rash, encephalitis, hepatitis, myelo-suppression, and interstitial pneumonitis [11,96]. The virus was first isolated from the lymphocytes of immune-compromised patient in 1986 [97]. It belongs to the beta-herpes subfamily, and it is closely related to CMV and HHV-7, all of these beta -herpesviruses are widely distributed in human populations. Human herpesvirus-6 and -7 are also called the Roseola viruses and are the causal agents of roseola infantum (also known as *Exantema subitum*), a febrile illness that is characterized by fever and skin rash during early childhood [98].

4.1 Human herpesvirus-6 (HHV-6)

HHV-6 is a large DNA virus 200 nm in diameter, with a linear double-stranded DNA genome [99]. Clinically, HHV-6 infections are mostly mild or subclinical, however, complications like seizures, respiratory, otitis, or GIT complications, and rarely hepatitis and encephalitis have been reported [100,101]. HHV-6 is infections mostly occur before 2 years of age, saliva is the most likely mode of transmission. Like other herpesviruses; HHV-6 persists in the host in a latent form; and its sero-prevalence in the adult populations is up to 95% [102,103].

Though the precise site of latency of the virus in the body is not well known, the salivary glands and bronchi represent the most likely sites of latency, in addition, neurons, and glial cells were also found to be sites of HHV-6 latency [104]. HHV-6 is infection was frequently reactivated in immune-suppressed renal transplant patients [105]. The virus could be transmitted through renal transplantation; however, infection mainly results from reactivation of the recipient's endogenous (latent virus), due to the high sero-prevalence rate of the virus in the general population [102,103].

HHV-6 was found to be a cause of infection in renal transplant recipients [106-108]. However, most infections are asymptomatic after renal transplantation [109,110]. In addition, viral DNA was frequently detected in peripheral blood mononuclear cells in asymptomatic renal transplant patients [111]. However, detection of HHV-6-specific antigens by immune-histochemistry in kidney biopsy were found to be associated with renal pathological conditions, like acute or chronic allograft rejection or nephropathy [107,112].

Reactivation of HHV-6 usually occur in the first month following transplantation and though HHV-6 infections in renal transplant recipients are usually mild, however, symptomatic and

even fatal HHV-6 infections have been reported [113].

There are several diagnostic methods; most importantly; quantification of viral DNA by PCR in blood, plasma or serum samples, however, there is no well-established HHV-6 VL thresholds used to recognize the levels of virus replication and establishing symptomatic infection [114-116].

In one study HHV-6 infection was observed in 8 of 49 (16.3%) RTRs (increasing VL over three months); their mean PTP was 6.4±3.5 months, 75% (6 out of these 8 patients) had biopsy-proven renal allograft rejection (P<0.001), and all of them (100%) were symptomatic (p=0.002), with 50% had fever, 25% had skin rash, and another 2 of 8 (25%) patients had upper respiratory tract infection. Viral loads (VL) were high (median viral load $4.5x10^4$ copies/mL blood), (p<0.001) [117]. In other studies, HHV-6 infection has been detected in 38-55% of kidney transplant recipients [107,118].

4.2 Human herpesvirus-7 (HHV-7)

Member of the beta herpesvirus subgroup was first isolated in 1990 in the blood of a healthy subject [119]. It is a ubiquitous virus with the primary infections occur early during childhood, and thus >90% are sero-positive [120]. HHV-7 establishes latent infections in the monocytes [121]. It reactivates following organ transplantation [122-124]; HHV-7 was found to be associated with graft rejection or impaired renal function, bone marrow suppression, and higher risk CMV disease [125-127].

Patients had CMV disease are at increased risk to have HHV-7 DNA than those who had asymptomatic CMV infection (31% versus 0%, P=0.13) [128]. In a study in kidney transplant recipients, patients with CMV and HHV-7 co-infection were at increased risk to develop CMV disease than those who had CMV infection only [129].

A recent study conducted by our team, investigated CMV, HHV-6 and HHV-7 infections together in kidney transplanted patients and found that co-infections increased the risk of nephropathy and allograft rejection. Also, roseola viruses increase the frequency and pathological effect of CMV infection in RTR (unpublished data).

4.4 Human Herpes Virus-8 (HHV-8)

HHV-8 or called Kaposi's sarcoma-associated herpes virus (KSHV) is the causal agent of all forms of Kaposi's sarcomas (KS), including post-transplant KS. HHV-8 is a gamma-herpesvirus of the genus Rhadinovirus, which are group of transforming viruses and have the ability to cause tumors in their hosts [130]. KSHV can be found in SOT recipients in a prevalence of 0.5 to 5%, which depends on the geographical origin, the rate of occurrence is 1,000-fold more common in SOT than in the healthy subjects [131].

Occurrence of KS among SOT is mainly associated with the use of immuno-suppressive therapy (especially calcineurin inhibitors), as evidenced by the remission of KS lesions following the reduction or withdrawal of the immunosuppressive therapy [132-135]. Several studies noted the reactivation of HHV-8 in the transplanted recipients [136,137]. HHV-8 was found to reactivate among SOT who were sero-positive before transplantation and high number of sero-negative subjects, including children, were found to sero-convert to HHV-8 after transplantation [138].

In renal transplantation, the duration of immunosuppression and its intensity, and HHV-8 sero-positivity pre-transplantation all increased the risk of KS occurrence, which usually starts 13 months post-transplantation [139].

A study conducted on a 70-year-old kidney transplanted woman who was suffering from purplish, macular rash on her lower limbs without any pain or pruritus. On examination there was large cutaneous purplish infiltrative plaques on the lower limbs highly suggestive of KS [140].

5- Varicella-zoster virus (VZV)

VZV is a ds-DNA virus and a member of herpes-virus family, and has the ability for life-long latency in the cranial nerves or dorsal nerve-root ganglia and persists in the subjects for life after primary infection, and it could be the second most common viral infection in SOT recipients (after CMV), reaches up to 29%. VZV occurs in about 11% of SOT recipients within the first 4 years of transplantation due to the long-term immune-suppressive therapy [141-144].

The incidence of VZV was increased among SOT receipts used Mycophenolate Mofoetil. VZV commonly occurs in the first 6 months post-transplantation; however, it can manifest longer after transplant. VZV infection in RTRs mainly results from reactivation rather than a primary infection, and severe sequel occurs [145,146].

VZV infection causes two clinical different disease forms, vesicular lesions on the trunk, head and extremities, characterize primary disease (varicella or chickenpox), the second form is herpes zoster (shingles) which is characterized by very painful unilateral vesicular eruption, which rarely might disseminate [147].

VZV or shingles occurs with an incidence of 1.5-3.0 cases/1000 in the general population annually and it is mainly related to age with incidence rising to 10 cases/1000 in subjects over 65 years of age. Incidence of VZV in SOT recipient increases 10-100 times, reaching up to 1-12% [148,149].

In one study included 240 patients, VZV prevalence was 3.33%, which is a lower prevalence as compared to other studies that had reported a high prevalence [150]. These findings showed that VZV infection was higher in males, however, another study showed that VZV was higher in females [151]. All of the patients who developed zoster infection had a previous history of VZV infection before kidney transplantation. The risk rate and severity of zoster infection is mainly related to the degree of the immune-suppression [147,152,153].

In other study, the prevalence rate of VZV in kidney transplants was 3.51%. However, female gender was considered as a risk factor for developing zoster infection. Majority of patients in this study had zoster infection in the first post-transplantation year. Only 4 patients developed VZV lately after transplantation, so that the median time of onset was 2.13 years. However, other previous studies showed that the onset of VZV infection after SOT could be between 2 and 92 months [141,143,154,155].

6- Adenovirus (ADV)

ADV belongs to the Adenoviridae family, in the past; ADV have made continuous challenges and wide range of clinical manifestations. ADVs are classified into 7 species, from A to G [156,157]. More than 71 types were reported according to the gene bank of human ADV genotype classification [158].

First isolated from the adenoids over 60 years ago, and these human ADVs were known to cause a wide spectrum of diseases, including gastroenteritis, kerato-conjunctivitis, upper and lower respiratory tract infections, hemorrhagic cystitis, and it produce in vitro cytolysis in these tissues [159].

ADV is the causative agent of around 5-10% of childhood febrile diseases. In an immuno-competent host, ADV infection occurs as mild, and self-limited upper respiratory tract infections. Most people have positive serologic evidence of previous adenovirus infections by the age of 10 years [160]. After the primary infection, adenovirus develops life-long latent infection in the lymphoepithelial tissues [159].

In the immuno-compromised hosts, adenovirus infections are among a spectrum ranging from asymptomatic viral shedding to a fatal-disseminated disease [159]. In the SOT, usually the primary site of ADV infection is related to the type of transplanted organ. Some of the signs and symptoms occur in the lung, liver, kidney, and small bowel transplantations, which included pneumonia, nephritis, hepatitis, enteritis, hemorrhagic cystitis, and rarely fatal-disseminated disease [161].

In RTRs, most common clinical manifestation is acute hemorrhagic cystitis and, less commonly pneumonia, with about 17% fatality rate [162]. ADV infections occur as either primary infection or reactivation of a previous infection, and presents as pneumonitis, nephritis, hemorrhagic cystitis or colitis and diarrhea in less than 2% of ADV cases, also the infection might become systemic and cause multi-organ failure [163-165].

In RTR adenovirus infections usually were shown very early after transplantation, and presented with very low absolute lymphocyte counts, and these patients might develop more severe complications and disseminated disease, for this reason lymphocyte counts could be used as a predictor for adenovirus disease and patient's outcome [166]. In addition, ADV infection in renal transplantation can be suspected when there are decoy cells (DC) in Pap-stained urine cytology however, significantly less common than polyomaviruses [167,168].

A study conducted on 71 RTRs Revealed that ADV viremia has been detected in the plasma samples of 21% of the RTRs (15 out of 71) [169]. Other studies showed that ADV infection can range from 5 to 22% [170,171].

Other study was case report study on 68-year-old man had renal transplantation, developed fever to 40 °C and rigors, macroscopic hematuria, diarrhea, respiratory symptoms, and conjunctivitis. This was followed by deterioration of the graft function. Testing of the CSF by PCR was negative for CMV, EBV and HSV, then urine sample collected near the onset of macroscopic hematuria returned PCR positive for adenovirus. Subsequent blood PCR testing was also positive [172].

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Correspondence to Dr. Asmaa B. Al-Obaidi
E-mail: asmaa.viro@gmail.com,
asmaa.viro@ced.nahrainuniv.edu.iq