High Prevalence of Viral Genomes and Multiple Viral Infections in the Myocardium of Adults With “Idiopathic” Left Ventricular Dysfunction

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Background—For a long time, enteroviruses have been considered to be the most common cause of acute viral myocarditis (MC), with possible transition from MC to dilated cardiomyopathy (DCM). Recent investigations have shown, however, that other viruses are also frequently encountered in MC patients, suggesting that persistence of various virus species may play a pathogenic role in the transition from MC to DCM. The purpose of this study was to screen endomyocardial biopsies (EMBs) from patients with “idiopathic” DCM for the presence of viral genomes by using polymerase chain reaction (PCR) to assess the frequency of cardiac viral infections that may be involved in the pathogenesis of the disease.

Methods and Results—EMBs were obtained for PCR analysis from 245 consecutive patients (median left ventricular ejection fraction, 35.0%; range, 9% to 59%). PCR and reverse transcription–PCR were performed to detect the genomic sequences of enterovirus (EV), adenovirus (ADV), human cytomegalovirus (HCMV), herpes simplex virus, Epstein-Barr virus (EBV), human herpesvirus 6 (HHV-6), parvovirus B19 (PVB19), and influenza A and B viruses. Myocardial inflammation was assessed by histological and immunohistological analyses. Viral genomes could be amplified from EMBs of 165 (67.4%) of the 245 DCM patients: EV/H11005 23 (9.4%), ADV/H11005 4 (1.6%), PVB19/H11005 126 (51.4%), HHV-6/H11005 53 (21.6%), EBV/H11005 5 (2.0%), HCMV/H11005 2 (0.8%), including n/H11005 45 cases (27.3%) with multiple infections. Active or borderline myocarditis according to the Dallas classification did not exist in any case. Lymphocyte and macrophage infiltrates were not significantly different in virus-positive versus virus-negative patients.

Conclusions—Viral genomes were frequently detected in EMBs of patients with systolic left ventricular dysfunction. Our data suggest that myocardial persistence of various viruses, often presenting as multiple infections, may play a role in the pathogenesis of DCM far more frequently than suspected so far. (Circulation. 2005;111:887-893.)

Key Words: cardiomyopathy • myocarditis • viruses • muscles • heart diseases

For many years, enteroviral infections of the heart have been associated with the development of dilated cardiomyopathy (DCM), which can occur as a late sequela of acute or chronic viral myocarditis,¹² because of either viral persistence³ or a chronic immune process initially triggered by a viral infection. By use of molecular genetic methods, enteroviral (EV) and adenoviral (ADV) genomes have been detected in 10% to 35% of analyzed endomyocardial biopsies (EMBs) of both disease entities (myocarditis and DCM).⁴⁻⁵ EV infections have been reported to be an important cause of morbidity and mortality during the natural course of DCM.⁶⁻⁸ A role of viral infections in the pathogenesis of DCM was also suggested by the significant improvement of heart failure symptoms and left ventricular ejection fraction (LVEF) observed in virus-positive patients with “idiopathic” LV dysfunction after antiviral treatment with interferon-β (IFN-β).⁸ IFN-β led to clearance of enteroviral and adenoviral genomes in these cases. Recently, we have observed a high frequency of a wide spectrum of cardiotropic viruses in the clinical setting of myocarditis, with viral genomes detectable in 71% of the patients analyzed.⁹ Parvovirus B19 (PVB19) was the most frequent pathogen, at 50%, whereas EV and ADV genomes were detected in 13% and 8% of consecutive patients, respectively. The purpose of the present study was to analyze the prevalence of a broad spectrum of cardiotropic viruses, including EV and ADV, in adults with “idiopathic” LV dysfunction, because a high frequency of such latent virus persistence would allow us to expand the concept of viral origins to a far broader subset of DCM patients than on the basis of EV and ADV data alone.
Median stroke volume index, mL/min 36 (21, 59)
Median cardiac index, L/min
Median EF, % 35 (17, 55)
Median left ventricular end-diastolic pressure, mm Hg 12 (5, 25)
Right/left ventricular branch block 18/67 (7.5/27.3)
Implantable cardioverter defibrillator/pacemaker 23/19 (9.4/7.7)
Amiodarone 33 (13.5)
Antithrombotic agents 132 (53.9)
Spironolactone 211 (86.1)
Diuretics 225 (91.8)
ACE inhibitors or angiotensin receptor blockers 237 (96.4)
Median diastolic blood pressure, mm Hg 80 (70, 80)
Median systolic blood pressure, mm Hg 120 (110, 140)
Pericardial effusion, % 14 (5.7)
Median time from onset of symptoms to EMB, mo 17.5 (2.0, 108.0)
White 245 (100)
Male 178 (72.5)
Median age, y 52 (32, 66)
Right/left ventricular branch block 18/67 (7.5/27.3)
Median left ventricular end-diastolic pressure, mm Hg 12 (5, 25)
Median EF, % 35 (17, 55)
Median cardiac index, L/min
Median stroke volume index, mL/min 36 (21, 59)
Median mean pulmonary artery pressure, mm Hg 17 (11, 35)
Echocardiography
Median left atrium 44 (33, 55)
Median left ventricular end-diastolic diameter 65 (52, 78)
Median left ventricular end-systolic diameter 52 (37, 67)
Median fractional shortening, % 18 (10, 32)
Median mitral valve E-point to septal separation 16 (5, 25)
Global wall motion abnormality 237 (96.7)

Data are presented as the median value (10th, 90th percentile) or No. (%) of subjects.

Methods

Patients
Between July 2001 and April 2003, 245 patients with clinically suggested DCM underwent EMB in our institution after angiographic and echocardiographic exclusion of coronary artery disease and other possible causes of cardiac dysfunction (eg, valve diseases, hypertension, or systemic diseases with known cardiac involvement). All patients gave written informed consent for EMB analysis to further elucidate a possible myocardial origin of their disease. The clinical diagnosis of DCM was taken into consideration in all patients who presented with idiopathic global or local/regional LV dysfunction and/or dilated LV in association with symptoms of heart failure (NYHA functional class II–IV) in spite of medication with ACE inhibitors, diuretics, spironolactone, glycosides, or β-blockers. Eighty-two percent of the patients (n=201) presented with reduced systolic LVEF (<50%), whereas in 18% of patients (n=44), LV diameters were increased >63 mm. In these patients, global systolic LV function was only mildly decreased (EFmean, 50% to 59%), with regional wall motion abnormalities. The demographic and clinical characteristics of the patients are shown in Tables 1 and 2.

EMB and Right-Heart Catheterization
Eight EMBs were obtained from the right side of the ventricular septum of each patient with a flexible biotope (Westmed) via the femoral vein approach. Two EMBs were used for the histological evaluation according to the Dallas criteria16 and immunohistological evaluation of intramyocardial inflammation,11 respectively, whereas the remaining 4 EMBs were subjected to DNA and RNA extraction for the amplification of viral genomes. After the EMBs were obtained, the patients underwent right-heart catheterization. A thermodilution Swan-Ganz catheter was used to measure right atrial (RA, mm Hg), right ventricular (RV, mm Hg), and pulmonary arterial (PA, mm Hg) pressures. Standard 2D and M-mode echocardiography were performed 1 day before or on the day of obtaining EMBs in all patients. For each echocardiogram, LV diastolic (LVEDD) and systolic (LVESD) dimensions were measured by M-mode echocardiography in the parasternal long-axis view using the leading-edge method. Percentage fractional shortening was calculated in a standardized manner.

Etiologic Investigations

Detection of Viral Genomes by Nested PCR
DNA and RNA were extracted from frozen heart muscle tissue probes. Polymerase chain reaction (PCR)/reverse transcription PCR (RT-PCR) was performed for the detection of enteroviruses (including coxsackievirus and echovirus), adenovirus,12 parvovirus B19,9,13 human herpesvirus type 6,13 human cytomegalovirus,14 Epstein-Barr virus,15 influenza virus A and B,16 herpes simplex virus 1 and 2,17 and hepatitis virus C.18 In addition, DNA was extracted from peripheral blood cells (PBLs) to exclude a systemic infection with PVB19, EBV, and HHV6. As a control for successful extraction of DNA and RNA from heart muscle tissue, oligonucleotide sequences were chosen from the DNA sequence of the GAPDH gene.19

Histological and Immunohistological Analysis of Infiltrating Lymphocytes
For histological analysis of myocardial inflammation, paraffin-embedded EMBs were analyzed according to the Dallas classification. Immunohistological analysis of infiltrating immunocompetent cells in frozen sections was performed as published elsewhere.11,20

Serological Investigations
Because a lack of correlation with biopsy findings has been reported for most cardiotropic viruses, only a PVB19 serological analysis was performed in a subgroup of 178 patients, using remcomBlot Parvovirus-B19-IgG (Mikrogen).

Statistical Analysis
Statistical analysis was performed using JMP Statistical Discovery Software, Version 3.1.6 (SAS Institute, Inc.). All results are presented as median values (10th, 90th percentile), except when stated otherwise. Qualitative data were compared by conducting the χ² test. A
probability value (2 sided) of $P<0.05$ was considered statistically significant.

Results

PCR Analysis
PCR amplified viral genomes in $n=165$ of 245 EMBs (67.4%) from the patients with the presumptive clinical diagnosis of DCM (Figure). Of these EMBs with positive detection of viral genomes, 126 (51.4%) were positive for PVB19, 53 (21.6%) for HHV6, 23 (9.4%) for EV, 4 (1.6%) for ADV, 5 (2.0%) for EBV, and 2 (0.8%) for HCV, including 45 samples (27.3%) with multiple infections: 26 (15.8%) with PVB19 and HHV6, 9 (5.5%) with EV and PVB19, 3 (1.8%) with EV and HHV-6, 1 (0.6%) with ADV and PVB19, 2 (1.2%) with PVB19 and EBV, 1 (0.6%) with HHV6 and EBV, 2 (1.2%) with EV, PVB19, and HHV6, and 1 (0.6%) with ADV, PVB19 and HHV6 (Figure). With regard to HHV6-positive patients, sequence analysis identified HHV6 type B but no type A in any case. Influenza A, influenza B, herpes simplex virus type 1, and human cytomegalovirus genomes were not detected. PCR analysis of blood samples drawn at the time of biopsy revealed no significant systemic virus infections or reactivations with PVB19 and HHV6. Whereas PVB19 genomes were not detected in PBLs of any patient, HHV6-specific DNA was found in 3 (5.6%) of the HHV6-positive patients. EBV-specific sequences, in contrast, were detected in 23 (14.1%) of the 165 blood samples of virus-positive patients. Neither positive nor negative EBV-PCR results for PBLs correlated with the respective findings for EMBs. Negative EBV-PCR results for EMB despite the positive detection of EBV genomes in the blood samples suggests that contamination of biopsies by blood-cell–derived viral genomes is rare and thus not a source of contamination of EMB virus analysis. With the exception of a high (80%) PVB19 infection rate in the subgroup of young patients <25 years of age, the other age groups had similar constant rates between 51% and 59% (see Table 5).

Histopathology and Immunohistochemistry
Histological analysis did not show active or borderline myocarditis in any of the samples analyzed. In the immunohistological stainings, neither T-lymphocytic or macrophage infiltrates nor endothelial expression of cell adhesion molecules (HLA-I/ICAM-1) distinguished between virus-positive and virus-negative patients (Table 3). However, numbers of lymphocytes and macrophages were increased (>7 cells/mm²) in both virus-positive and virus-negative tissues (Table 3), and adhesion molecule expression correlated with infiltrating inflammatory cell numbers. Virus type–specific analysis of inflammatory cells or adhesion molecules was not performed because of the rather small size of the virus subgroups.

PVB19 Serology
Positive PVB19 IgG titers were detected in 99 of 104 (95.2%) PVB19 PCR–positive and 29 of 74 (39.2%) PVB19 PCR–negative patients. Forty-five patients (60.8%) without detectable PVB19 genome in the EMB had a negative IgG serology (Tables 4 and 5). The frequency of age-dependent PVB19-IgG titers reflected the reported prevalence of PVB19 IgG antibodies in the population. Positive PVB19 IgM titers were not detected in any of the patients. With regard to PVB19 PCR data, the diagnostic value of PVB19 serology was calculated as follows: sensitivity (95.2%), specificity (60.8%), predictive value for PVB19 infection (68.2%), predictive value for exclusion of PVB19 infection (93.8%).
Discussion

High Prevalence of Cardiac Viral Genomes in DCM Patients

Enteroviruses, in particular group B coxsackieviruses, have been detected in EMBs of myocarditis and DCM patients.22,23 They have been linked to the transition from myocarditis to DCM and are considered to be important prognostic factors in DCM.7,8,24 Despite the introduction of sensitive molecular biological methods for the detection of EV genomes, the incidence of EV infections in DCM was rather low, and thus, the hypothesized viral cause of DCM appeared to be confined to a small subset of DCM patients. However, the recent detection of non-EV viral genomes (eg, PVB19) in myocarditis patients presenting with a sudden onset of cardiac symptoms mimicking acute myocardial infarction9,25 raised questions about the total prevalence of any cardiotropic viruses in the myocardium of adults with “idiopathic” DCM. We report here on a high prevalence (67.4%) of viral genomes and multiple viral infections in the myocardium of 245 consecutive adult DCM patients. The screening of these patients showed EV and ADV genomes in only 23 (9.4%) and 4 (2.0%), respectively, of the EMBs. In contrast, PVB19 was positive in 126 (51.4%) and HHV6 in 53 (21.6%) of cases. Dual or multiple infections also occurred at a high rate, in 45 (27.3%) of patients. In only 32.6% of all patients was no viral genome detected. Systemic PVB19 infections were excluded by negative PVB19 PCR results for PBLs. Possible contamination of EMBs with blood-derived PVB19 or EBV genomes was not observed.

The high prevalence (67.4%) of viral genomes and multiple viral infections in the myocardium of patients with DCM was unexpected, although viral causes have long been discussed for patients with the unexplained ventricular dysfunctions referred to as “idiopathic” DCM.1,2,26 This term, which constituted the final diagnostic result obtained in the majority of patients with the clinical phenotype of DCM, is unlikely to remain satisfying in the long run. It rather reflects the insensitivity of the diagnostic tools used so far and may in part be because former studies have not taken into consideration a broad panel of potentially cardiotropic viral agents during the diagnostic procedure, but have instead relied on EV and ADV only. PVB19 and HHV6 genomes, detected at frequencies of 51.4% and 21.6%, respectively, in our analysis, have previously been reported in cardiomyopathies of childhood.13,27–29 In adults, however, PVB19 and HHV6 have so far been detected as possible pathogenic agents only in rare cases of myocarditis and DCM.9,25,30

Virus-Associated Intramyocardial Inflammation

Conventional histological analyses did not detect active or borderline myocarditis in any of the 245 patients. This observation confirms that routine histological analysis is too insensitive to detect myocardial inflammation accurately in the chronic phase of the disease or if only a few samples are used for routine analysis.31 With regard to the immunohistochemical analysis of infiltrating immune cells, viral genomes were detected in similar frequencies regardless of the number with blood-derived PVB19 or EBV genomes was not observed.

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Table 3. Histological and Immunohistological Findings in Virus-Positive and Virus-Negative Patients With DCM

<table>
<thead>
<tr>
<th>Virus Genomes (PCR)</th>
<th>Negative (n=80 [32.6%])</th>
<th>Positive (n=165 [67.4%])</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active/borderline myocarditis</td>
<td>0/0</td>
<td>0/0</td>
<td>NS</td>
</tr>
<tr>
<td>Immunohistology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean T lymphocytes (CD3+)</td>
<td>3.8 (0.7, 6.5)</td>
<td>3.5 (0.5, 7.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean macrophages (27E10+)</td>
<td>2.3 (0.7, 7.5)</td>
<td>3.0 (0.7, 6.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Enhanced lymphocytic infiltration (&gt;7 cells/mm²)</td>
<td>7.9% (10.7, 71.4)</td>
<td>12.4% (9.1, 20.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean T lymphocytes (%, CD3/mm²)</td>
<td>13.0% (8.4, 17.3)</td>
<td>9.3% (8.7, 18.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean macrophages (%, cells/mm²)</td>
<td>15.0% (8.4, 17.3)</td>
<td>9.3% (8.7, 18.8)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are presented as the median value (10th, 90th percentile) or No. (%) of subjects.

Table 4. Correlation of PVB19 IgG Serology With PVB19 PCR (n=178)

<table>
<thead>
<tr>
<th>PVB19-PCR</th>
<th>PVB19-IgG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>(n=128)</td>
</tr>
<tr>
<td>Negative</td>
<td>(n=50)</td>
</tr>
<tr>
<td>Positive</td>
<td>99 (95.2)</td>
</tr>
<tr>
<td>Negative</td>
<td>5 (4.8)</td>
</tr>
<tr>
<td>Negative</td>
<td>(n=74)</td>
</tr>
</tbody>
</table>

Data are presented as No. (%) of subjects.
of lymphocytes or macrophages infiltrating the myocardium. This finding is consistent with the hypothesis that virus persistence is promoted if the antiviral immune response is inefficient, as discussed above, and that antocardiac autoimmunity ensues in some DCM patients despite virus elimination.32 Follow-up investigations are warranted to elucidate whether virus persistence or clearance is influenced by the host’s individual immune responses during the natural course of the disease and by antiviral treatment, thereby influencing the natural course of the disease.8

**Possible Consequences of Cardiac Viral Infection**

The detection of viral genomes in 67.4% of cases in a series of 245 DCM patients does not per se prove a causal role of any virus in the pathogenesis or further progression of the disease. However, these data strongly suggest that viral infections, which are not detected in normal hearts of multi-organ donors or valvular heart disease,33,34 may play a major role at some time during the pathogenesis of DCM. In addition to direct cytopathic effects of viruses such as EV or ADV, other virus-triggered pathomechanisms may be involved. Both PVB19 and HHV6 have been shown to infect various tissues, including vascular endothelial cells and mitotic fetal cardiomyocytes. High expression levels of the PVB19 and HHV6 receptors (P-antigen/α,β-integrin and CD46, respectively) on endothelial cells may facilitate infections of the coronary vascular endothelium with these viruses and thereby aggravate virus-induced cardiac pathological conditions.9 HHV6 may directly lyse and thus destroy target cells, or it may induce immune or autoimmune reactions as a consequence of HHV6-induced alterations of cytokine expression patterns. HHV6 is also able to modulate cell membrane receptors, leading to harmful tissue inflammation and/or immune suppression and preventing virus clearance.35 Indirect damage to primarily noninfectable cells and tissues (eg, cardiomyocytes) may originate from HHV6-induced complement activation and immune and/or autoimmune reactions.35 Notably, HHV6 is able to activate other viral infections, eg, those induced by EBV or PVB19, and thus may enhance the pathogenicity of these viruses.35 Even a small cardiac load of persisting viral genomes may theoretically sustain further progression of the disease, either by direct low-level cytopathic effects of virus-encoded proteins or by indirect virus-induced sequelae, such as local chronic myocardial inflammation,36 local release of cytokines,37,38 disruption of dystrophin,39 modulation of cellular signaling pathways,40 or alterations of the extracellular matrix. Even if a virus was cleared spontaneously during the natural course of the disease, the initial viral infection may nevertheless have caused a minor but irreversible structural damage to the myocardium during the early stages of the disease that later slowly progresses to more severe systolic dysfunction and ventricular dilatation. This would resemble the slow remodeling process observed after myocardial infarction, and because the primary viral pathogenic agent would no longer be detectable in the myocardium, the diagnostic procedures would yield virus-negative “idiopathic” DCM.

**Multiple Viral Infections: Possible Origins and Consequences**

In 27% of the virus-positive patients, dual or multiple infections of the myocardium with different combinations of viruses were detected. The pathways for viral entry into the myocardium have not yet been fully delineated, especially not for cases of multiple viral infections. Induction of the coxackievirus adenovirus receptor (CAR), a common receptor for both coxsackieviruses and adenoviruses, has been observed in DCM but not in other cardiomyopathies.41 This provides a basis both for cardiac infection with any CAR-dependent virus (EV/ADV) and also for the existence of dual infections by the respective viruses,7 which are further influenced by distinct coreceptors for the 2 viruses. Another common receptor (CD46) shared by 2 otherwise unrelated viruses (HHV6 and CAR-independent group B ADVs) has recently been identified.32 In line with the distribution patterns of the virus receptors on the surface of either cardiomyocytes or vascular endothelial cells, the respective viruses have been localized within distinguishable cellular compartments (myocardium or the coronary vascular endothelium) by in situ hybridization.25,43,44 Induction and modulation of cardiac receptor and coreceptor expression patterns may explain not only the existence of organ infections by multiple viruses but also the highly variable presentation and outcome of patients with viral heart diseases. Genetic determinants of receptor expression, immune reactions, or myocardial structure certainly also influence the disease course. Viral infections of different cellular compartments of the heart, however, should have grossly different effects on the hemodynamic course and clinical complaints, depending on whether the patient suffers from a primarily myocardial (eg, EV, ADV) or coronary vascular endothelial (eg, PVB19, HHV6) infection.

The hemodynamic course of DCM is variable and not predictable. In patients with dual infections, however, clearance of only one virus could explain the hemodynamic improvement of patients in whom another viral genome is still detectable in follow-up biopsies during the course of the disease.55 This hypothesis is consistent with our own experience when following the natural course of dual myocardial viral infections (eg, PVB19 and HHV6) and also when treating such patients with IFN-β. Spontaneous or IFN-β-induced clearance of one of the 2 viruses was often associated with hemodynamic improvement, despite the persistence of the other virus. Thus, restricted virological diagnostic procedures not addressing the possibility of multiple viral infections of the myocardium may be a key reason for the controversial results reported in the past for the clinical course of patients with virus-associated heart disease.

**Virus Serology**

Several reports have stressed the fact that serological analysis for virus IgM or IgG antibodies does not correlate with local virus infection of the myocardium of most cardiotropic viruses analyzed so far, and therefore the absence or presence of antiviral antibodies does not allow any conclusions about infection of the myocardium.46 Corresponding data analyzing PVB19 and HHV6 serology in association with heart diseases...
have not been available so far. PVB19 and HHV6 are common causes of human infections worldwide. Approximately 30% to 50% of children below age 15 years are seropositive, a prevalence that rises to >90% in the elderly.21

Subgroup analysis (n = 178) detected HHV6 IgG antibodies in 90% of patients regardless of their HHV6-PCR results for EMBs. No diagnostic information could be drawn from this analysis (data not shown). As expected, sensitivity, specificity, and predictive value for positive detection of PVB19 antibodies of IgG type were low because of the high prevalence of PVB19 antibodies in adults and did not provide additional diagnostic information for the diagnosis of PVB19 infection of the myocardium. PVB19 serology had, however, a high negative predictive value of 93.8% for PVB19-negative biopsies, because PVB19-positive serology was found in only 5 (4.8%) of 50 PVB19 PCR EMB-negative patients.

Conclusions

In view of the high prevalence (67%) of viral genomes in the myocardium of 245 consecutively analyzed DCM patients as reported here, viral infections of the myocardium should be considered as possible triggers or contributing factors for the development of the disease in a large fraction of the DCM patients. These results underline the need for biopsy-based molecular virological analyses in patients with heart failure of unknown cause. The unexpected high prevalence of viral genomes further suggests that viral myocarditis may be a more frequent initial trigger for the development of DCM than assumed so far and that a large fraction of DCM patients may have passed through viral myocarditis with subclinical presentation. Pathomechanisms induced during the early stages of unrecognized viral myocarditis may then be responsible for later progression to DCM by remodeling or immunopathology after elimination of the primary viral agent. Thus, the present data are consistent with a novel pathogenic concept of “viral” DCM. In light of the efficacy of antiviral treatment in patients with chronic heart failure associated with enteroviral or adenoviral persistence, antiviral strategies may have therapeutic potential in a large fraction of DCM patients.

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References


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