

Original article

Antiviral therapy of primary cytomegalovirus infection with vascular thrombosis in immunocompetent adults

Traitement antiviral de la primo-infection à cytomégalovirus compliquée de thrombose vasculaire chez les adultes immunocompétents

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Received 25 July 2015; received in revised form 11 October 2015; accepted 29 December 2015

Available online 2 February 2016

Abstract

Background. – Vascular thromboembolism (VTE) complicating cytomegalovirus (CMV) primary infection is increasingly reported in immunocompetent adults. No guideline is, however, currently available for the management of these infections and particularly for the antiviral therapy indication.

Methods. – We performed a literature review of VTE complicating CMV primary infection in immunocompetent adults using PubMed.

Results. – Sixty-nine case patients of VTE complicating CMV primary infection were reported. The main sites of venous thrombosis were the splanchnic veins (30 patients) or those of the lower limbs (18 patients). One-third of patients presented with pulmonary embolism (25 patients). Forty-nine patients (76%) had at least one VTE risk factor, inherited or acquired thrombophilia for 37 patients (58%), and another risk factor for 27 patients (42%). Only 11 patients received an antiviral therapy. A positive outcome was observed in all patients.

Conclusion. – We suggest that antiviral therapy should be considered for patients presenting with severe VTE, VTE with a negative outcome despite anticoagulation, severe organ involvement, or for patients managed in the intensive care unit.

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Keywords: Cytomegalovirus; Thrombosis; Antiviral therapy

Résumé

Objectifs. – Les cas de primo-infections à cytomégalovirus (CMV) compliquées d'un accident thromboembolique chez des adultes immunocompétents sont de plus en plus fréquents. Cependant, il n'existe pas de recommandation de prise en charge de ces infections, notamment concernant l'indication d'un traitement antiviral.

Patients et méthodes. – Une revue systématique de la littérature décrivant les cas d'accident thromboembolique compliquant une primo-infection à CMV chez des adultes immunocompétents a été effectuée sur PubMed.

Résultats. – Soixante-neuf cas d'accident thromboembolique compliquant une primo-infection à CMV ont été rapportés. Les thromboses touchaient principalement les veines abdominales (30 cas) ou celles des membres inférieurs (18 cas). Une embolie pulmonaire survenait chez un tiers des patients (25 cas). Quarante-neuf patients (76 %) avaient au moins un facteur de risque thromboembolique, thrombophilie acquise ou constitutionnelle chez 37 patients (58 %) et autre facteur de risque chez 27 patients (42 %). Onze patients seulement ont reçu un traitement antiviral. L'évolution a été favorable chez tous les patients.

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Conclusion. – Nous proposons de réserver le traitement antiviral aux cas d'accident thromboembolique sévère, d'accident thromboembolique d'évolution défavorable sous anticoagulation, ou aux cas de primo-infection avec atteinte viscérale sévère ou pris en charge en réanimation.
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Mots clés : Cytomégalo­virus ; Thrombose ; Traitement antiviral

1. Introduction

Vascular thrombosis is a rare complication of cytomegalovirus (CMV) infection in immunocompromised patients. Thrombosis is increasingly reported during CMV primary infection in immunocompetent adults. However, there is currently no guideline on the management of such infections and particularly on the duration of anticoagulation and on the benefits of an antiviral therapy.

We performed a literature review of thrombosis associated with CMV infection in immunocompetent patients.

2. Materials and methods

We performed a literature review of vascular thromboembolism (VTE) complicating CMV primary infection in immunocompetent adults. We carried out a search on PubMed and included French and English articles published before December 2014. We used “Cytomegalovirus Infections” and “Embolic and Thrombosis” as keywords. We did not include articles on immunocompromised patients such as HIV-infected patients or transplant recipients, nor did we include articles on children aged under 15 years. We also reviewed the articles included in the reference list of all selected articles.

3. Results

Overall, we included 49 case reports ([Appendix I–available online](#)) with a total of 69 patients (41 women and 28 men), mainly young adults (median age 35 years, range 17–83 years).

3.1. Clinical diagnosis

CMV infection diagnosis was frequently made on the basis of aspecific viral symptoms (mainly prolonged fever). Patients presented with asthenia, cough, headache, arthromyalgia, skin rash, lymphadenitis, hepatomegaly, or splenomegaly. The results of the laboratory tests often revealed inflammatory syndrome, thrombocytopenia, mononucleosis-like syndrome, and hepatitis.

The time between viral symptom onset and thrombosis substantially varied. Most patients (40 of the 55 patients for whom such data was available) presented with thrombosis after viral symptom onset (from two days to six months, median 14 days). Thirteen patients presented with concomitant thrombosis and viral symptoms while thrombosis appeared before fever onset in two patients.

The main sites of venous thrombosis were the splanchnic veins (30 patients, involving the portal vein [18], mesenteric

vein [13], splenic vein [9], and hepatic vein [2]), or the lower limbs (18 patients). Other venous sites (ovarian vein, internal jugular vein, vena cava, cerebral vein) were reported in the case reports. Arterial thrombosis was reported in only two patients (superior mesenteric artery and digital ischemia) and transient ischemic attack in one patient. One-third of patients also presented with pulmonary embolism (PE) (25 patients).

3.2. Virological diagnosis

Serological tests with IgM level, IgG level, IgG avidity assay, pp65-antigenemia, and CMV PCR were performed in various combinations to confirm CMV recent infection.

CMV primary infection was confirmed on the basis of the Center for Disease Control and Prevention (CDC) criteria [1] in 49 patients: direct detection of CMV (by PCR, antigenic test, or culture) in 39 patients, IgG seroconversion in 19 patients, detection of low-avidity IgG in five patients (in some cases direct viral detection and serology were performed concomitantly). The virological diagnosis was incomplete for 15 patients; it was only based on positive IgM ($n = 11$) or positive IgM and IgG on one single dosage ($n = 4$). The virological diagnosis method was not described for five case patients.

3.3. Associated VTE risk factors

A complete screening for thrombophilia was performed in 64 patients out of 69.

Forty-nine patients (76%) had at least one VTE risk factor, in addition to CMV infection ([Table 1](#)). Thirty-seven of them (58%) had thrombophilia, either inherited or acquired, and 27 (42%) had other predisposition, mostly oral contraception or smoking habits. Overall, 26 patients (38%) had several VTE risk factors (thrombophilia for seven patients, other risk factors for three patients, and both thrombophilia and other risk factors for 16 patients). Fifteen patients (22%) did not have any VTE risk factor.

3.4. Anticoagulant treatment

Treatment was described for 51 patients and 48 received an anticoagulant treatment, either heparin or vitamin K antagonists (VKA). Treatment duration, when reported ($n = 20$), was six months ($n = 10$) or three months ($n = 5$) for most patients. Various durations (three weeks to two years) were reported for five patients. Anticoagulant treatment was discontinued without any radiological evaluation of the thrombus for most patients.

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