Diagnosis of Viral Infections Using Myxovirus Resistance Protein A (MxA)

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Abstract

BACKGROUND: Myxoma resistance protein 1 (MxA) is induced during viral infections. MxA testing could be helpful to differentiate between viral and bacterial infections.

METHODS: A prospective multicenter cohort study was performed in pediatric emergency departments. MxA blood values were measured in children with confirmed viral or bacterial infections, uninfected controls, and infections of unknown origin. First patients were used to determine MxA threshold for viral infection. The diagnostic performance of MxA was determined by using receiver operating characteristic (ROC) analysis. Sensitivities (Se), specificities (Sp), and positive and negative likelihood ratios (LR+, LR–) were calculated.

RESULTS: The study included 553 children; 44 uninfected controls and 77 confirmed viral infections (mainly respiratory syncytial virus and rotavirus) were used to determine an MxA threshold at 200 ng/mL. In the 193 other patients with confirmed infections and uninfected controls (validation group), MxA was significantly higher in patients with viral than in those with bacterial infections and uninfected controls (P < .0001). The area under the ROC curve (AUC) were 0.98, with 96.4% Se and 85.4% Sp, for differentiating uninfected from virus-infected patients and 0.89, with 96.4% Se and 66.7% Sp, for differentiating bacterial and viral infections. MxA levels were significantly higher in patients with clinically diagnosed viral versus clinically diagnosed bacterial infections (P < .001). Some patients with Streptococcus pneumoniae infections had high MxA levels. Additional studies are required to elucidate whether this was due to undiagnosed viral coinfections.

CONCLUSIONS: MxA is viral infection marker in children, at least with RSV and rotavirus. MxA could improve the management of children with signs of infection.

WHAT'S KNOWN ON THIS SUBJECT: Myxovirus resistance protein A (MxA) is a protein induced during viral infections. A few small-scale studies have suggested that MxA could be used as a marker of viral infection in clinical routine practice.

WHAT THIS STUDY ADDS: This study involves the largest patient population thus far and confirms the usefulness of MxA for diagnosing viral infections in children consulting the emergency department in a clinical routine setting.

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Dr Engelmann analyzed and interpreted the data, prepared figures and tables, and drafted the manuscript; Dr Dubos participated in study design, patient recruitment, data analysis, and drafting of the manuscript; Dr Lobert performed laboratory analyses, participated in data analysis, and critically revised the manuscript; Drs Houssin and Degas participated in patient recruitment and data analysis; Drs Sardet and Decoster participated in patient recruitment; Dr Dewilde performed laboratory analyses and revised the manuscript critically; Dr Martinot participated in study design, patient recruitment, and critical revision of the manuscript; Dr Hober designed and supervised the study and participated in drafting of the manuscript; and all authors approved the final manuscript as submitted.


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Viral infections are frequent, especially in children. Distinguishing early between viral and bacterial infections in children is difficult based only on clinical or routinely available biological findings, with subsequent management consequences. Indeed, children may present with a variety of clinical signs, including fever, rash, respiratory symptoms, and meningitis that can be of viral or bacterial origin. Therefore, when in doubt, antibiotic treatments are frequently prescribed. This diagnostic uncertainty leads to unnecessary antibiotic therapy and hospitalization that could be avoided if a specific and reliable biomarker of viral infection were available. In addition to reducing health care costs, the reduction of unnecessary antibiotic therapy would help to limit the development and spread of antimicrobial resistance. Unfortunately, at present a specific biomarker for viral infection is not available in routine diagnostics. During viral infections a cellular response is elicited that includes the secretion of type I interferons (IFNs). Type I IFNs are involved in innate immune responses and have immunomodulatory, antiproliferative, and antiviral functions. Although sometimes used as viral biomarker, type I IFNs did not show good diagnostic performance because of a short half-life in body fluids. The antiviral activity of type I IFNs is mediated by the induction of several proteins, including myxovirus resistance protein A (MxA). MxA was first described as antiviral protein in influenza virus infection and was subsequently shown to have a broad antiviral activity against a wide range of RNA and some DNA viruses. MxA belongs to the superfamily of GTPases and can be induced by type I or type III IFN signaling via the Janus-activated kinase/signal transducer and activator of transcription pathway.

It has been proposed that MxA could be used as a marker of viral infection in the clinical setting. Small-scale clinical studies have found promising results showing that MxA levels enable the differentiation of viral and bacterial infections. The present prospective multicenter study was undertaken to confirm these findings in routine practice conditions in a larger patient population including different clinical syndromes and infections with different bacterial and viral pathogens.

**METHODS**

**Patients**

Patients were recruited from the pediatric emergency department (ED) of the University Hospital, Lille, France, and of the General Hospitals of Lens and Lomme, France, between April 2004 and March 2007. Patients were identified according to their clinical symptoms, and routine diagnostic workup was performed. Inclusion criteria were as follows: children aged 0 to 16 years with clinical symptoms compatible with a viral or bacterial infection or a noninfectious disease for the control group (ie, full blood count, C-reactive protein [CRP]). Systematic testing for bacterial and viral infections was not part of the study design. Microbiological testing was prescribed by the physician.

**Microbiological Methods**

Routine immunochromatographic assays were used for detection of rotavirus and adenovirus in stool specimens. Routine immunofluorescence techniques were used to detect antigens of respiratory syncytial virus (RSV); influenza virus A and B; parainfluenza virus type 1, 2, and 3; and adenovirus in respiratory specimens. Enterovirus RNA was detected in cerebrospinal fluids using reverse transcriptase polymerase chain reaction (primers AAGCAGGTGGTCTCGGCCG and ATTGTACCATAAGGCAGCCA) until
June 2006 and real-time reverse transcriptase polymerase chain reaction there after (primers CCCTGAAATGCGGCTAATC, ATTTGCACCATATAAGCGAGCA and probe FAM-AACGCGACTACT TTGGGTGTCCGTGTTT-TAMRA) (adapted from Verstrepen et al12).

Bacterial infections were detected by culture from usually sterile fluids or serological tests in the case of Mycoplasma pneumoniae, Chlamydia pneumoniae, and Leptospira.

Detection of MxA Protein in Blood

Two separate monoclonal antibodies, one directed to the C-terminal (clone 1302.5.32) and the other to the N-terminal (clone 1302.34.16.2.44) portion of Mx protein (provided by Jeanne Harvey, Bayer Diagnostics Corporation, Emeryville, CA) were used respectively as detector and capture antibodies in a sandwich-type immunoassay.13 Briefly, blood was drawn into 0.5-mL lithium heparin tubes (Vacutainer, Terumo, Italy); 25 µL of whole blood was lysed using an ascorbic acid lysis buffer (ACS: 180, Chiron Diagnostics, les Ullys, France). When necessary, the lysates were stored at −80°C until the assay was performed; 200 µL of test samples, standards, or controls were incubated in plastic tubes simultaneously with 100 µL Mx Lite Reagent (N-hydroxysuccinimide-activated-dimethyl-acridinium-ester-labeled detector antibody) and 200 µL of solid phase (paramagnetic particles-conjugated antibody, Chiron, Alameda, CA). The tubes were shaken by using a Multi-tube Vortexer (Model 4010, Chiron Diagnostics, Villeneuve d’Ascq, France). These mixtures were incubated for 30 minutes at 37°C. The solid phase-bound immune complex was separated with a magnetized separator rack (Magic Rack, Chiron, Villeneuve d’Ascq, France) for 3 minutes at room temperature. The separated pellets were then washed twice in 1 mL of distilled water, and the unbound antigen or antibody was discarded by decanting the rack. Relative Luminescence Units were measured with a MLA-II luminometer (Chiron, Villeneuve d’Ascq, France) and then transformed in ng/mL using a master curve.

Statistical Analysis

The population of included patients was first described. The different groups were compared by using Pearson’s χ² test, Mann-Whitney U test, or Kruskal-Wallis test as appropriate. Second, MxA blood levels between the first controls and patients with confirmed viral infections were analyzed to determine the best MxA threshold for the diagnosis of viral infections. Third, the remaining patients with confirmed infections and uninfected controls were used as validation group to determine the statistical performances of MxA as a diagnostic marker of viral infection. Receiver operating characteristic (ROC) curve analyses were performed, and sensitivity (Se), specificity (Sp), positive and negative likelihood ratios (LR+, LR−), and 95% confidence intervals (CI) were calculated by using a cross-tabulation with the predefined MxA threshold and various other thresholds. Fourth, the MxA distribution was compared regarding the different pathogens detected. Fifth, the diagnostic performance of a combination of MxA and CRP values for differentiating confirmed viral and confirmed bacterial infections was assessed in 2 ways: first, MxA values >200 ng/mL and CRP values <40 mg/L were defined as indicators of viral infection; second, a ratio of MxA/CRP was calculated, and a threshold of ≥20 was defined as indicator of viral infection secondary to ROC curve analysis and Se, Sp, LR+, and LR− were calculated.

A P value <.05 was considered statistically significant. SPSS (21.0 version) and MedCalc for windows version 12.5 (MedCalc Software, Ostend, Belgium) were used for statistical analyses.

RESULTS

Data from 585 patients were collected; 32 were excluded subsequently. Exclusion criteria were recent infection (n = 2), coinfection with a bacterial and a viral pathogen (n = 2), missing data (n = 26), and inclusion criteria not fulfilled (n = 2). A total of 553 patients (median age: 2 years [range: 0.006–15]; 52% male) were included in the study. Their characteristics, clinical syndromes, and viral or bacterial diagnoses are shown in Table 1. Analyses were focused on patients with infections confirmed by pathogen detection (viral infections, n = 133; bacterial infections, n = 48; uninfected controls, n = 133). Data of unconfirmed infection groups were analyzed to show the usefulness of MxA testing in clinical practice where most infections are not microbiologically confirmed.

Determination of the MxA Threshold

The first 44 uninfected control patients (ie, 31 trauma, 6 intoxications, 3 blood tests for surgery, 3 ingestion/inhalation of foreign body, 1 malaise) and 77 patients with confirmed viral infection (ie, 50 RSV, 24 rotavirus, 2 adenovirus, 1 parainfluenza virus type 1) were used for MxA threshold determination (Fig 1A and 1B). MxA blood levels in the group with documented viral infection (median 1465 ng/mL) were significantly higher than in the control group (median: 14 ng/mL, P < .0001). The area under the ROC curve of MxA levels was 0.999 (95% CI: 0.996–1.00). Choosing a best threshold value at 200 ng/mL, the Se and Sp for identifying patients with viral infections were 97.4% (95% CI: 90.9–99.6) and 100% (95% CI: 91.9–100), respectively.

Validation of MxA as a Marker of Viral Infection

The remaining patients with confirmed infections and uninfected
controls (n = 193) were included in the validation group. The 56 confirmed viral infections were 26 RSV, 24 rotavirus, 3 adenovirus, 2 enterovirus, 1 combined adenovirus, and parainfluenza virus infection. The 48 confirmed bacterial infections were 16 Escherichia coli, 9 Streptococcus pneumoniae, 3 Staphylococcus aureus, 4 group A Streptococcus (1 patient with scarlet fever, including tonsillitis and typical exanthema with positive rapid test; 1 patient with a tonsil phlegmon and positive culture and rapid test of a swab; 1 patient with abscess and positive culture from a swab; and 1 patient with tonsillitis and positive rapid test), 3 group B Streptococcus, 3 Neisseria meningitidis, 2 Salmonella enteritidis, 2 Chlamydia pneumoniae, 1 Enterococcus, 1 Proteus mirabilis, 1 Leptospira, 1 Mycoplasma pneumoniae, 1 combined Chlamydia pneumoniae and Mycoplasma pneumoniae infection, and 1 combined E coli and S pneumoniae infection. The 89 uninfected controls presented to the ED with trauma (n = 59), intoxication (n = 22), malaise (n = 3), digestive troubles (n = 2), or other noninfectious reasons (n = 3). MxA levels in the uninfected control group (median 32 ng/mL) were significantly lower than in the patients with confirmed viral infection (median 1373 ng/mL) (P < .0001). Furthermore, MxA levels were significantly lower in patients with confirmed viral infection than in those with confirmed bacterial infection (median 1416 ng/mL vs. median 800 ng/mL, respectively) (P < .0001).
with confirmed bacterial infection (median 101 ng/mL) than in patients with confirmed viral infection ($P < .0001$) (Fig 2A).

The area under the ROC curve for differentiating uninfected from patients with confirmed viral infection was also high in the validation population, at 0.98 (95% CI: 0.96–1.00) (Fig 2B). With an MxA threshold at 200 ng/mL, Se, Sp, LR+, and LR− were 96.4% (95% CI: 87.7–99.5), 85.4% (95% CI: 76.3–92.0), 6.60 (95% CI: 3.98–10.94), and 0.04 (95% CI: 0.01–0.16), respectively. Results were similar, when patients were stratified according to age: the area under the ROC curve was 0.98 (95% CI: 0.94–1.01) for patients up to 2 years ($n = 56$) and 0.98 (95% CI: 0.95–1.00) for patients 2 years or older ($n = 89$).

Additionally, when considering patients with confirmed bacterial and confirmed viral infection, the area under the ROC curve for differentiating between those patients was at 0.89 (95% CI: 0.82–0.96) (Fig 2C). With an MxA threshold at 200 ng/mL, Se, Sp, LR+, and LR− were 96.4% (95% CI: 87.7–99.5), 66.7% (95% CI: 51.6–79.6), 2.89 (95% CI: 1.93–4.33), and 0.05 (95% CI: 0.01–0.21), respectively (Table 2). When patients were stratified according to age, the area under the ROC curve for differentiating patients with confirmed bacterial and confirmed viral infection was 0.77 (95% CI: 0.62–0.92) for patients up to 2 years ($n = 58$) and 0.94 (95% CI: 0.88–1.01) for patients 2 years or older ($n = 46$). The diagnostic performances of MxA were also calculated for a range of other thresholds (Table 2).

High blood levels of MxA were mostly present in both rotavirus and RSV infections (Fig 3A). The median MxA levels were not different among the bacterial pathogens, even if MxA levels in *S pneumoniae* infections showed a wide distribution of values with some high values (Fig 3B).

CRP levels were measured in a subgroup of patients with confirmed viral or bacterial infections ($n = 47$ [84%] and $n = 33$ [69%], respectively) as part of the routine diagnostic workup. As expected, CRP levels were higher in patients with confirmed bacterial infection (median: 51 mg/L) than in those with confirmed viral infection (median: 10 mg/L; $P < .0001$). Patients with confirmed viral and bacterial infections can be clearly distinguished when plotting MxA levels with CRP levels (Fig 4A). Using a combination of MxA and CRP with a MxA level $>200$ ng/mL and CRP level $<40$ mg/L as indicator of viral infection (box in Fig 4A), area under the ROC curve, Se, Sp, LR+, and LR− for differentiating between bacterial and viral infections were 0.84 (95% CI: 0.75–0.94), 80.9% (95% CI: 66.7–90.8), 87.9% (95% CI: 71.8–96.5), 6.67 (95% CI: 2.63–16.89), and 0.22 (95% CI: 0.12–0.40), respectively.
The current study shows the high performance of blood MxA analysis for the diagnosis of viral infections in a large number of children with RSV and rotavirus infections and with various clinical presentations. To date, it is the first prospective multicenter study that evaluated MxA performance in routine practice conditions in children.

Biological markers such as CRP or procalcitonin have been used for several years in routine practice to help physicians in the management of patients, to rule in or rule out bacterial infections, especially to decide if an antibiotic therapy is indicated.14–17 However, there is an overlap of CRP values between children with bacterial and viral infection.18 Although procalcitonin is specific of bacterial infection,18 it has been validated for children in only a few clinical situations in routine practice. A specific marker of viral infection in clinical practice could be particularly useful, but is currently not available, in clinical settings where viral infections are frequent, such as in pediatric EDs.

In our study, MxA values in patients with viral infection were significantly higher than in patients with bacterial infection or uninfected controls (Fig 2A). Some patients of the uninfected control group showed elevated MxA levels. This could be due to undiagnosed asymptomatic viral infections because control patients did not undergo systematic screening for viral infections. The same might be the explanation for the lower area under the ROC curve of MxA for differentiating viral and bacterial infections in children up to 2 years compared with older children.

Previous experimental studies or studies with smaller cohorts of patients have shown the good performance of blood MxA testing for patients with viral infections.5,6,9,19 The thresholds chosen differed from 1 study to another, ranging from 36.7 ng/mL to 500 ng/mL,5,19,20 related to methodologic MxA detection differences, ROC curve analyses, or desired Se or Sp. In our study, MxA levels above the 200-ng/mL threshold predicted a viral infection with useful LRs for practice. However, other thresholds could be used in pursuit of a high Se or

<table>
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<th>MxA thresholds, ng/mL</th>
<th>Se, % (95% CI)</th>
<th>Sp, % (95% CI)</th>
<th>LR+, % (95% CI)</th>
<th>LR−, % (95% CI)</th>
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<tr>
<td>130</td>
<td>100 (93.6–100.0)</td>
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<td>200</td>
<td>96.4 (87.7–99.5)</td>
<td>66.7 (51.6–79.6)</td>
<td>2.89 (1.93–4.33)</td>
<td>0.05 (0.01–0.21)</td>
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<tr>
<td>500</td>
<td>87.5 (75.9–94.8)</td>
<td>77.1 (62.7–88.0)</td>
<td>3.02 (2.25–6.48)</td>
<td>0.16 (0.08–0.53)</td>
</tr>
<tr>
<td>800</td>
<td>78.6 (65.6–88.4)</td>
<td>85.4 (72.2–93.9)</td>
<td>5.39 (2.68–10.83)</td>
<td>0.25 (0.15–0.42)</td>
</tr>
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</table>

a Patients with confirmed viral and bacterial infection of the validation group.
b no confidence interval.

FIGURE 3
Blood MxA values differentiated by pathogens. Blood MxA values of infected patients depending on the viral (A) or bacterial pathogen (B). P value for the comparison of bacterial pathogens = 0.46 (Kruskal-Wallis test). The horizontal bar shows the median. Because of the logarithmic scale, MxA values were transformed as follows for graphical representation: value shown in the graph = MxA value + 1.
a high Sp. In fact, the choice of an optimal threshold value can depend on the clinical situation, namely, whether the aim is to diagnose a viral infection (high Se), to exclude a bacterial infection (high Sp), or to differentiate between bacterial and viral infection (best Se/Sp combination).

The strength of this multicenter study is based on the large recruitment of children during emergency admission, with narrow 95% CIs for most of our results. The identification of a pathogen in 43% of infectious cases (181 of 420) is probably the main limitation. However, not identifying the pathogen responsible for the disease is common in pediatric EDs. Therefore, we included the patients without pathogen identification as “clinically diagnosed” infections. The MxA values in the clinically diagnosed viral infection group showed a wider range compared with the confirmed viral infection group. This indicates that a number of patients in the clinically diagnosed viral infection group (probably those with low MxA values) were erroneously classified as viral infections, underlining the usefulness of MxA testing even if the range of MxA values might differ depending on the infecting virus or the viral load.

Although the sensitivity of microbiological testing has improved, there is a need for rapid biological markers with good diagnostic performance that fill the lack of performance and availability of rapid microbiological testing and provide rapid and reliable results. The prospective design of the study has limited the number of missing data. However, because blood testing for other biological markers was not systematic, comparison with other biological markers was not possible, except for CRP. Procalcitonin was less frequently tested at that time and is indicated in our institutions only in rare situations. A limitation of the study is the bias to enteric and respiratory virus infections. Although these viruses account for the majority of viral infections with which children present to the ED and because infections with other viruses were rare in our study population, additional studies are needed to confirm that infections with other viruses also present with high MxA levels as has been suggested by some small-scale studies. Future studies are also needed to address the usefulness of MxA in other acute viral infections with, for example, herpesviridae, measles, mumps, rubella, and influenza viruses. Furthermore, it will be important to study MxA as a diagnostic marker in the context of chronic viral infections, such as hepatitis C, hepatitis B, and HIV. To date, some studies have investigated the relationship of MxA response or MxA polymorphisms and treatment responses in chronic...
hepatitis B and C. It would be interesting to study how the MxA response differs in acute versus chronic phases of chronic viral infections such as hepatitis B, hepatitis C, and HIV.

Another interesting field is antiviral vaccines. Vaccination with yellow fever vaccine has been shown to induce a MxA response. The MxA response after vaccination with live virus versus inactivated vaccines and first dose versus booster dose should be compared. Whether levels of this new marker reflect differences in the vaccine-induced immunity needs to be examined in future studies. Our study has included the highest number of patients with bacterial infections (48 of 420 infections) of published MxA studies. Nevertheless, the high diversity of bacterial pathogens detected limits the conclusions that can be drawn for a single pathogen.

An elevated MxA level would be an argument for a viral infection and could facilitate the decision not to treat with antibiotics. In our study, MxA levels were much higher in patients with viral infections than in patients with bacterial infections or in uninfected patients, regardless of the clinical picture, pathogen, and site of infection. However, in some bacterial infections, MxA production can be detected. This can be explained by bacterial and viral coinfections that sometimes occur. Furthermore, MxA protein remains detectable until ~10 days after viral infection (as shown for vaccination with yellow fever virus). We hypothesized that the relatively high MxA values observed in cases of S pneumoniae infections might be due to a frequent undiagnosed viral infection preceding the bacterial pneumonia. In this context, it might help to use a marker of bacterial infection as well. In our study, CRP was only measured if requested by the treating physician. Therefore, CRP is only available in 6 cases with S pneumoniae infection. Of these, 5 had an elevated CRP, 3 with low MxA levels as expected for a bacterial infection and 2 with high MxA levels. One of the patients with high CRP and MxA values had pneumonia and symptoms of laryngitis in parallel. We thus hypothesize that a viral coinfection was present, although no viral pathogen was documented. No further information was available for the second patient. Finally, 1 patient had a high MxA value with negative CRP. We can only speculate that this might be a viral infection that was misdiagnosed as bacterial. Although larger datasets with systematic testing for viral and bacterial pathogens are needed to conclude on the reason for the high MxA values in S pneumoniae infections, we reasoned that a combination of both CRP and MxA can help separating bacterial from viral infections.

Blood MxA testing used alone would likely have the same limitations as all biological markers. However, combining MxA detection with a marker specific for bacterial infection, such as CRP (Fig 4) or procalcitonin, could be of greater predictive value and allow more reliable differentiation between viral and bacterial infections than using a marker of bacterial infection alone. For example, high MxA and low CRP would allow exclusion of bacterial infection and confirm viral infection. The additional confirmation of viral infection would be particularly important if the consequence is the decision not to hospitalize the patient or not to treat with antibiotics. The distribution of MxA versus CRP values suggested that calculating a ratio between the 2 and using a threshold of 20 as indicator of viral infection would result in an even better marker (Fig 4B and 4C).

A recent study showed that the measurement of MxA messenger RNA is also useful for the diagnosis of viral infections in febrile patients after allogeneic stem cell transplantation. The use of this marker of viral infection is therefore also promising in specific patient populations at high risk of infectious complications. The recent development of a sandwich-type enzyme-linked immunosorbent assay for human MxA protein in blood in a 96-well plate format could facilitate the automation of MxA measurement and its introduction in the routine diagnostic laboratory.

CONCLUSIONS

This large study in a pediatric populations shows that MxA is a valuable diagnostic marker for viral infections, primarily RSV and rotavirus, in children. In combination with a marker specific for bacterial infection, MxA could improve the management of children with signs of infection.

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