Journal of the Neurological Sciences 325 (2013) 46–50

Contents lists available at SciVerse ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Early blood-based microbiological testing is ineffective in severe stroke patients

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ARTICLE INFO

Article history:
Received 16 July 2012
Received in revised form 20 November 2012
Accepted 27 November 2012
Available online 28 December 2012

Keywords:
Stroke
Systemic complications
Acute stroke
Microbiology immune system depression
Management of stroke

ABSTRACT

Background and purpose: Patients with severe acute stroke are at high risk for systemic infections which are associated with an increase in morbidity and mortality; nevertheless current guidelines do not recommend prophylactic antibiotic therapy. Sensitive detection of pathogens in the blood is desirable to guide early antibiotic therapy. We studied the yield of blood culture testing and microbiological PCR-based methods for early detection of post-stroke bacteremia.

Methods: Serial blood culture tests either during the first fever episode (>38.5 °C) or 24 h after admission were performed every 12 h for up to 96 h after admission. Additionally, microbiological PCR-based techniques for the detection of microbiological pathogens were performed once during the first fever episode prior to initiating antibiotic treatment.

Results: 21 severely affected acute stroke patients deemed at high risk for systemic infections (median (interquartile range (IQR)) at admission NIHSSS 19 (15–30) were enrolled; 20 patients were intubated within 5 h after ICU admission. All patients developed clinical signs and laboratory constellations compatible with systemic infections within 36 h after admission. However, no patient had pathogenic bacteria either in serial blood culture analyses during the first 96 h after admission or by PCR-based techniques.

Conclusions: Very early bacteremia seems not to be a feature of severe stroke in patients despite signs of early immune system depression and frequent subsequent evidence of infection including pneumonia. Consequently our data suggests, that routine early blood-based standard or molecular microbiological assays do not reveal bacteremia, this finding questions the usefulness of their routine performance in this context.

1. Background and purpose

Patients with acute stroke are at high risk for infections. Particularly, early onset respiratory tract infections are of a major concern because they contribute substantially to morbidity and mortality after stroke [1–5]. Especially the risk for post-stroke infections for patients with major stroke and patients treated on an ICU is highly increased [6]. Because the efficacy of early nonselective preventive antibiotic therapy in stroke patients is currently unclear [7–9], current stroke guidelines do not generally recommend an early nonselective preventive antibiotic treatment for treating early respiratory infections after stroke [10,11].

Establishing early markers is a promising approach to identify stroke patients who might benefit from preventive antibiotic treatment. In this context, standard markers of infection like C-reactive protein are of limited value due to unspecific post-stroke elevations and lacking diagnostic cutoff levels [12,13]. To date, only surrogate markers including reduced HLA-DR expression on monocytes at day one after stroke, clinical severity (NIHSSS) or infarct volumes are available for the identification of patients at high risk for post-stroke infections [14–17]. Another, more specific approach would be the direct and early identification of a causative pathogen which would allow a targeted antibiotic treatment. For this purpose accurate and fast microbiological tests are needed. Commercial PCR-based technique for the early and specific detection of frequent causative pathogens in blood has been established [18,19]. The value of this diagnostic tool particularly under consideration of a possible bacteremia in patients with stroke is unknown.

The primary aim of our study was to evaluate the presence of bacteremia in severe stroke patients with a high risk of developing post-stroke infections. The secondary aim was, to test for the yield of

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http://dx.doi.org/10.1016/j.jns.2012.11.014

rapid PCR-based microbiological assays during the first fever episode of severe stroke patients to detect a bacteremia in severe stroke patients.

2. Methods

All study procedures were performed after obtaining informed consent from the patient or a legal guardian according to a protocol approved by the independent local ethics committee of the Medical Faculty of the University of Heidelberg. We prospectively enrolled 21 consecutive adult patients with an acute, severe ischemic or hemorrhagic stroke. All patients were primarily treated on a neurological intensive care unit (NICU) or transferred to the NICU within 24 h after stroke-onset. Patients with local or systemic infections within two weeks prior to admission, coma upon admission, advanced neoplastic disease, the need for an early hemicraniectomy or other planned surgical procedures were excluded.

To confirm the clinical diagnosis of stroke and to distinguish between ischemia and hemorrhage all patients underwent cranial CT or MRI on admission. All patients had a follow-up image according to the clinical routine. Volumes of cerebral infarcts and hematomas were measured on a 24–36-hour follow-up imaging using a free software tool (OsiriX 3.9.2, University of Geneva, Switzerland). Infarct etiologies were classified according to the TOAST criteria [19].

Serial blood culture testing was started in all patients, either 24 h after admission or if body temperature increased ≥38.5° Celsius (C), whichever event came first. The first blood culture was collected before initiating the antibiotic therapy. At the first fever episode urine and tracheal secretion specimens were obtained for microbiological work-up as part of the clinical routine before initiating the antibiotic treatment. Blood was obtained via direct venipuncture (e.g. antecubital vein) applying sterile techniques and 10 mL blood was inoculated to an aerobic and anaerobic liquid culture medium, respectively (BACTEC PLUS, BD Biosciences, Heidelberg, Germany). Cultures were incubated for 5 days (BACTEC, BD Biosciences, Heidelberg, Germany), positive cultures were analyzed according to approved in-house hospital standard techniques (including identification by VITEK2 (Biomerieux, Nuertingen, Germany) or MALDI TOF (Bruker, Madison, WI, USA) and automated antimicrobial susceptibility testing (VITEK 2). Blood specimens for cultures were performed every 12 h for a total of 7 cultures per patient. Tracheal secretion specimens were obtained via endotracheal aspiration in an unprotected suction trap. Urinary specimens were obtained via sterile cannulation of the indwelling urinary catheter. Specimens were plated manually (endotracheal aspiration) or semi-automated (Previ Isola, Biomerieux, Nuertingen, Germany), cultivated and identified according to standard techniques. A urinary tract infection was defined by the presence of a pathogen with $>10^4$/ml colony forming units. Tracheal specimens were defined positive if abundant presence of one typical pathogen was reported.

Additionally, 10 mL of the first blood sample was examined using a commercially available PCR-kit established for sensitive early detection of a panel of bacteria in septic patients according to the manufacturer's instructions (Light cycler® SeptiFast, Roche, Grenzach-Wyhlen, Germany) [20]. We also studied the yield of another in-house PCR-based technique (for protocol see supplementary file 1) for detection of bacteremia established in the Department of Infectious Diseases-Microbiology and Hygiene, University Heidelberg.

For both microbiological PCR analyses 10 mL of EDTA-anticoagulated blood was drawn in patients either 24 h after admission or during a body temperature rise of >38.5 °C. These blood samples were collected before initiating the antibiotic therapy. Blood for PCR was shock frozen and stored at −80 °C until further processing.

Quantitative HLA-DR expression analysis was performed 24 and 96 h after NICU admission using the QuantiBRITE Anti-HLA-DR-PE/Anti-Monocyte-PerCPCy5.5 kit according to the manufacturers' instructions (Becton Dickinson, Heidelberg, Germany).

2.1. Routine clinical procedures

In case body temperature exceeded 38.5 °C, empirical intravenous (iv) antibiotic treatment was started according to our hospital's standard. Routinely, isolated pathogens were tested for resistance against the initiated antibiotic therapy. Standard antibiotic therapy was piperacillin/tazobactam and clindamycin and in case of allergy against penicillin moxifloxacin according to our in-house ICU standard.

Furthermore, physical and medical antipyretic treatment was initiated after the first occurrence of a body temperature >38.5 °C according to current stroke guidelines aiming to prevent a temperature of 38.0 °C [10,11].

Clinical follow-up was performed by NIHSS-scoring every 8 h. If low blood pressure indicated treatment with catecholamines (to increase blood pressure), the decision on the use of catecholamines was left to the treating physician.

Laboratory parameters were obtained as part of the clinical routine every 24 h after admission (CRP, fibrinogen, procalcitonin (PCT), white blood counts (WBC)). Body temperature was routinely measured every other hour via a temperature probe in the urinary catheter or an infrared ear-thermometer.

2.2. Definitions of infection

Infection was defined as previously reported [15] by the combination of the following 2 criteria during in-hospital stay: (1) presence of suggestive clinical and laboratory or radiological signs of infection (e.g. urinary tract symptoms, productive cough, pleuritic pain, dyspnea, tachypnea, fever, cultures positive for a pathogen, leukopenia [<4/L] or leukocytosis [>12/L], chest X-ray infiltrate during stay at NICU); (2) serum CRP >50 mg/mL, screening time was 96 h after inclusion to this study.

Systemic inflammatory response syndrome (SIRS) was diagnosed, if a patient fulfilled at least two of the following criteria: (1) temperature <36.0 °C or >38.5 °C, (2) tachycardia >90/min, (3) tachypnea (>30/min) or hypoventilation (PaCO2 ≤4.3 kPa/≤33 mmHg), (4) leukocytes <4000 or >12,000/nL [21].

In the absence of infiltrates on chest X-ray upper respiratory tract infection was diagnosed (e.g. tracheobronchitis). The combined occurrence of SIRS and infection was defined as sepsis. Sepsis with additional organ failure (e.g. acute renal failure) was defined as severe sepsis [21].

2.3. Statistical analysis

Normally distributed data are given as mean ± standard error of mean (SEM). Non-normally distributed or ordinal distributed data are given as median and interquartile range (IQR). Ordinal and non-normally distributed continuous data were analyzed using nonparametric tests (Wilcoxon rank sum test, Friedman test). Proportions and nominal data were compared with the use of chi-square tests. A two-sided significance level of 0.05 was regarded statistically significant. Exact confidence limits for binomial distributions (Clopper–Pearson) were calculated with use of the SAS®9.2 statistical software package.

3. Results

We prospectively enrolled 21 severely affected acute stroke patients over a period of 7 months (patient characteristics see Table 1). One patient died before the 96 h visit due to massive intracerebral hemorrhage. Median NIHSSS on admission was 19 (IQR 15–30). The 24 h FU-visit NIHSSS deteriorated in all patients due to sedation associated with invasive mechanical ventilation (38 (IQR 38–38)). The 96 h FU-visit NIHSSS was similar to the initial examination (19 (IQR 16–34), p = 0.73 for comparison with baseline). In accordance with