Cerebral microdialysis for detection of bacterial meningitis in aneurysmal subarachnoid hemorrhage patients: a cohort study

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Abstract

Introduction Bacterial meningitis (BM) is a severe complication in patients with aneurysmal subarachnoid haemorrhage (SAH). Clinical signs of meningitis are often masked by SAH-related symptoms, and routine cerebrospinal fluid (CSF) analysis fails to indicate BM. Microdialysis (MD) is a technique for monitoring cerebral metabolism in patients with SAH. A cohort study was performed to investigate the value of MD for the diagnosis of BM.

Methods Retrospectively, 167 patients with SAH in an ongoing investigation on cerebral metabolism monitored by MD were analysed for the presence of BM and related MD changes. Diagnosis of BM was based on microbiological CSF culture or clinical symptoms responding to antibiotic treatment, combined with an increased CSF cell count and/or fever. Levels of MD parameters before and after diagnosis of BM were analysed and compared with the spontaneous course in controls.

Results BM developed in 20 patients, of which 12 underwent MD monitoring at the time of diagnosis. A control group was formed using 147 patients with SAH not developing meningitis. On the day BM was diagnosed, cerebral glucose was lower compared with the value three days before (p = 0.012), and the extent of decrease was significantly higher than in controls (p = 0.044). A decrease in cerebral glucose by 1 mmol/L combined with the presence of fever ≥ 38°C indicated BM with a sensitivity of 69% and a specificity of 80%. CSF chemistry failed to indicate BM, but the cell count increased during the days before diagnosis (p < 0.05).

Conclusions A decrease in MD glucose combined with the presence of fever detected BM with acceptable sensitivity and specificity, while CSF chemistry failed to indicate BM. In patients with SAH where CSF cell count is not available or helpful, MD might serve as an adjunct criterion for early diagnosis of BM.

Introduction

Bacterial meningitis (BM) is a severe and cost-intensive complication in patients with aneurysmal subarachnoid haemorrhage (SAH) and requires immediate treatment. Although appropriate therapy with potent antibiotics is available, BM continues to be associated with a prolonged stay in the intensive care unit (ICU) and high morbidity [1]. External drainage of cerebrospinal fluid (CSF), frequently applied especially in patients with high-grade SAH, may raise the risk of infections of the central nervous system (CNS). The diagnosis is difficult in patients with SAH because the clinical signs of meningitis are often masked by SAH-related symptoms. Furthermore, an alteration in CSF composition known as aseptic meningitis is frequent after SAH and cannot reliably be distinguished from CSF changes caused by BM [2]. Routine microbiological and chemical analysis of CSF for the prediction or diagnosis of BM failed in patients with external drains [3]. Considering these restrictions and the risks associated with a delayed diagnosis of BM, additional tools to facilitate the early diagnosis of BM after SAH would be desirable.

Cerebral microdialysis (MD), an advanced neuromonitoring technique, gives online information on the metabolic state of the injured brain. This technique is mainly used to detect ischaemia-related changes for early diagnosis of symptomatic vasospasm in patients with SAH [4-6]. Additionally, it allows quantification of interleukins and thereby provides analysis of immunological processes within the brain, which may allow...
earlier therapeutic measures in the beginning of immunoreactive cascades and thereby improve outcome in these patients [7]. For investigating intracranial infections, the MD technique has only been used in animal models and two case studies in humans [8,9]. During experimental pneumococcal meningitis, a decrease in cortical glucose levels and an increase in local lactate production in the brain were observed [10]. Hence, the present study aimed to evaluate whether cerebral MD allows – besides the monitoring of ischaemia-related changes – the early detection of BM, and to assess its significance compared with CSF analysis and clinical changes.

Materials and methods

Patient population

Both this study and the underlying prospective investigation on cerebral metabolism were approved by the Local Research Ethics Committee at Charité Campus Virchow Medical Center, in accordance with the Declaration of Helsinki as revised in Edinburgh in October 2000. Written informed consent was obtained from the patient or their nearest family relative.

Table 1

Demographic and clinical characteristics of 167 patients following aneurysmal subarachnoid haemorrhage

|                      | All patients (n = 167) | Meningitis (n = 20) | Controls (n = 147) | p     |
|----------------------|------------------------|---------------------|--------------------|-------|
| Age                  | 50.8 ± 12.6            | 53.5 ± 9.7          | 50.4 ± 13.0        | 0.292 |
| Gender: male/female  | 46/121                 | 5/15                | 41/106             | 0.802 |
| Admission WFNS grade | 2.7 ± 1.6              | 3.6 ± 1.3           | 2.6 ± 1.6          | 0.009 |
| 0                    | 3 (2%)                 | 0 (0%)              | 3 (2%)             |       |
| I                    | 58 (35%)               | 2 (10%)             | 56 (38%)           |       |
| II                   | 21 (13%)               | 3 (15%)             | 18 (12%)           |       |
| III                  | 18 (11%)               | 2 (10%)             | 16 (11%)           |       |
| IV                   | 38 (23%)               | 8 (40%)             | 30 (20%)           |       |
| V                    | 29 (17%)               | 5 (25%)             | 24 (16%)           |       |
| Clinical group       |                        |                     |                    | 0.867 |
| Asymptomatic         | 66 (40%)               | 8 (40%)             | 58 (40%)           |       |
| AFND                 | 58 (35%)               | 6 (30%)             | 52 (35%)           |       |
| DIND                 | 43 (26%)               | 6 (30%)             | 37 (25%)           |       |
| Time SAH – surgery (hours) | 45.0 ± 74.4         | 61.0 ± 133.3        | 42.8 ± 62.3        | 0.519 |
| Fisher-score         | 3.0 ± 1.0              | 3.5 ± 0.6           | 3.0 ± 1.0          | 0.059 |
| Duration of microdialysis (hrs) | 165.4 ± 83.8        | 185.2 ± 96.8        | 162.8 ± 81.9       | 0.252 |
| Presence of CSF drainage | 77 (46%)              | 18 (90%)            | 59 (40%)           | 0.001 |
| ICU stay (days)      | 15.1 ± 9.3             | 20.6 ± 6.9          | 14.3 ± 9.4         | 0.003 |
| GOS at 6 months after SAH | 3.8 ± 1.4            | 4.0 ± 1.2           | 3.8 ± 1.4          | 0.889 |
| Mortality rate at 6 months | 20 (13%)              | 1 (6%)              | 19 (14%)           | 0.322 |

P values are given for comparison of patients developing meningitis and controls (calculated by Mann Whitney-U-Test or, for dichotomous data, by chi-squared test, exact versions).

AFND = acute focal neurological deficit; CSF = cerebrospinal fluid; DIND = delayed ischaemic neurological deficit; GOS = Glasgow outcome scale; ICU = intensive care unit; SAH = subarachnoid haemorrhage; WFNS = World Federation of Neurological Surgeons.
area lactate and glutamate levels are known to be elevated [14]. The remaining 167 patients were included in this analysis.

Bedside microdialysis
In all patients, cerebral metabolism had been measured by an MD catheter (CMA 70, CMA, Solna, Sweden); membrane length 10 mm; molecular weight limit of 20 or 100 kD) in the brain parenchyma of the corresponding vascular territory of the aneurysm, with the catheter tip being located about 1.5 cm from dura level. The correct positioning of the catheter tip within the vascular territory of the aneurysm was verified postoperatively by CT. Catheters were perfused with sterile Ringer’s solution at a flow rate of 0.3 μl/minute. The estimated recovery for the system is 0.65 to 0.72 (recovery in the two different catheter types is comparable for molecules up to 20 kD) [15,16]. On the outlet tube, perfusates were collected in microvials and analysed hourly at the bedside for up to 20 kD) [15,16]. The outlet tube, perfusates were collected in microvials and analysed hourly at the bedside for parameters of energy metabolism (glucose; pyruvate; lactate; lactate/pyruvate (L/P) ratio; lactate/glucose (L/G) ratio) as well as glycerol and glutamate, in a mobile photometric, enzyme-kinetic analyser (CMA 600, CMA, Solna, Sweden). MD was performed for 7 to 10 days after SAH, and daily medians of the microdialysate concentrations were calculated for each patient.

Data analysis
The MD and CSF data were collected during days 1 to 10 after SAH. Data in tables and text are expressed as mean ± standard deviation, if not otherwise specified. Statistical analysis was based on each patient’s daily median values for each MD variable and on daily CSF samples. Average microdialysate values given for a group of patients were established calculating the mean value of the patients’ individual daily medians for the MD parameters. Between group comparisons were performed by nonparametric Mann-Whitney U tests and chi-squared tests for dichotomous data (exact versions). Analysis of sequential data over time was performed using Wilcoxon signed-rank test. Sensitivity and specificity of changes in MD parameters for diagnosis of BM were evaluated in all the patients undergoing MD monitoring at the time of meningitis. They were calculated for MD changes alone and in combination with fever of 38°C of above. Results were displayed by receiver operating curves, and the cutoff value for MD changes that showed the highest sum of sensitivity and specificity was calculated. Statistics were calculated using SPSS 14.0 (SPSS Inc., Chicago, IL, USA) and R, Version 2.6.0 (The R Foundation for Statistical Computing, Vienna, Austria). Differences were considered statistically significant at p < 0.05.

Results
Patients
Results from 1.025 daily MD medians and 77 CSF samples in 167 patients were analysed. Twenty patients (12%) had been diagnosed with BM by the physician in charge. All of them fit this study’s criteria for meningitis and were included. At the time of meningitis 12 of the patients were undergoing MD monitoring and in eight patients MD values were available for the complete three-day-period before diagnosis of BM.

In 10 patients (50%), diagnosis of BM was based on microbiological CSF findings (six patients had MD monitoring at the time of diagnosis). Microbiological characteristics of these patients are shown in Table 2. In a further 10 patients, diagnosis was based on CSF changes and clinical symptoms responding to antibiotic treatment typically used for BM (four patients had MD monitoring at the time of diagnosis). One patient had already received antibiotic treatment before diagnosis of BM (in this case, BM was confirmed by microbiology). CSF values were available for 14 patients with BM. A control group was formed using 147 patients with SAH who did not develop any CNS infection during the observation period.
Risk factors and outcome in patients with SAH developing bacterial meningitis

Patients developing BM were more severely affected by the haemorrhage than controls (WFNS grade: \( p = 0.01 \)). This is most likely to be due to the fact that in patients with high-grade SAH a CSF drainage, known as a risk factor for BM, was present more frequently than in controls. Almost all patients with BM had CSF drainage (90%), but only 40% of patients not developing CNS infections had a CSF drainage (\( p < 0.001 \)). On the day of diagnosis of BM, a CSF drainage had been present for 7.63 ± 3.2 days (range 2 to 14 days), and the actual drainage had been present for 6.69 ± 3.4 days (range 1 to 14 days).

In this small group of patients with BM, mortality rate or neurological outcome at six months after SAH did not differ significantly from controls. ICU stay was prolonged by 38% in patients with BM (20.4 ± 7.6 vs. 14.8 ± 9.7 days after excluding patients who died during ICU stay; \( p = 0.003 \); Figure 1).

CSF and MD changes related to bacterial meningitis

During the time span from three days before to two days after diagnosis of BM, no significant changes in CSF glucose, lactate or protein concentrations were observed. CSF cell count, however, was significantly higher on the day of diagnosis than three (\( p = 0.028 \)) and two (\( p = 0.01 \)) days before. It should be mentioned that in some patients the diagnosis of BM was based on this elevation in CSF cell count, so the role of this parameter as an independent indicator of BM cannot be reliably evaluated in this study.

In cerebral extracellular fluid analysed by MD, changes in glucose and L/G ratio were observed. On the day BM was diagnosed, cerebral glucose was lower (\( p = 0.012 \)) and the L/G ratio higher (\( p = 0.036 \)) compared with three days before (Figure 2). The extent of decrease in glucose was significantly higher than in controls (\( p = 0.044 \)), while the course of L/G ratio did not differ significantly from the control group (MD changes at three days before diagnosis of BM, compared with randomly selected periods of three days in controls). The other measured parameters showed no significant changes during the three days before diagnosis of BM. During this period of time, there was no significant change in blood glucose concentrations in this group of patients, which would naturally have to be considered as a cause of changes in cerebral glucose, independent of meningitis (Figure 3).

The cutoff value for a decrease in MD glucose that showed the highest sum of sensitivity and specificity for indication of BM was 1 mmol/L. The diagnostic power of cerebral glucose changes and fever is summarised in Table 3. A decrease of 1 mmol/L over any time span identified BM with a sensitivity of 92% and a specificity of 50% (Figure 4), while the presence of fever (≥38°C) together with a glucose decrease of 1 mmol/L reached a sensitivity of 69% and a specificity of 80% (Figure 5).

Discussion

This study aimed to assess the value of cerebral MD for diagnosis of BM in patients with SAH. There are three major findings. First, ICU stay was prolonged by an average of six days in patients with SAH and BM. Second, CSF chemistry failed to indicate BM in the observed patients, although CSF cell count showed a significant increase. Third, a decrease in cerebral glucose by 1 mmol/L measured by MD combined with the presence of fever detected BM with a sensitivity of 69% and specificity of 80%.

| Causative agent                | Number of patients |
|-------------------------------|--------------------|
| Staphylococcus aureus         | 4                  |
| Coagulase-negative Staphylococci | 6              |
| S. epidermidis                | 2                  |
| S. warneri                    | 1                  |
| S. capitis                    | 1                  |
| Acinetobacter baumannii       | 1                  |
| Escherichia coli              | 1                  |

Bacteria were identified by microbiological culture of cerebrospinal fluid. In some patients, more than one organism was found.

Table 2

Microbiological characteristics of 10 patients with bacterial meningitis after aneurysmal subarachnoid haemorrhage.

Figure 1

Length of stay in the intensive care unit (ICU) in patients with aneurysmal subarachnoid haemorrhage (SAH). Box plot presenting ICU stay in patients with SAH and meningitis, and in patients with SAH and no infections of the central nervous system. Patients who died during the ICU stay were excluded. Boxes represent 25th, 50th and 75th percentiles; dots mark the outlier values. \( p \) values were calculated using Mann-Whitney U test (exact version).
Significance of CNS infections in patients with SAH

Hydrocephalus is a frequent complication after SAH and is usually treated by external CSF drainage, so this patient group is at risk of CNS infections [17]. The MD catheter itself might also be a port of entry for bacteria, but MD monitoring has not been reported to be associated with an increased risk of CNS infections [4,18,19]. With an incidence of between 1 and 9 per 100 patients, CNS infections are among the most commonly documented infections in neurointensive care units [17,20-22]. In a recent study in a large SAH population, meningitis/ventriculitis occurred in 5% of patients and was the fourth most common nosocomial infection after pneumonia (20%), urinary tract infections (13%) and bloodstream infec-

Cerebral extracellular glucose and lactate/glucose ratio in patients with aneurysmal subarachnoid haemorrhage (SAH) and bacterial meningitis. Individual courses of (a) cerebral extracellular glucose and (b) lactate/glucose (L/G) ratio in patients with SAH and bacterial meningitis. Daily median microdialysate concentrations on three days before diagnosis of meningitis and on the day of diagnosis are presented for those patients with a complete dataset for that period. Each line represents one individual patient. P values were calculated using Wilcoxon signed-rank test.

Diagnosis of bacterial meningitis in patients with SAH

Diagnosis of BM is usually based on clinical symptoms and changes in CSF composition [25]. These are, however, of limited predictive value even in patients without additional neurological disease [26]. In patients with SAH, clinical symptoms are even more unreliable, because most of the typical signs of meningitis such as headache, nuchal rigidity and altered mental status cannot safely be distinguished from SAH-related symptoms. Fever is also an unreliable diagnostic marker. Due to impaired cerebral temperature regulation after SAH, elevated body temperatures can also occur spontaneously or be absent in cases of severe infection. Additionally, respiratory and urinary tract infections are more frequent in these patients than BM, so suspicion of meningitis is often raised late if there are no typical clinical or CSF findings. However, CSF composition is frequently altered by biochemical reactions to the subarachnoid blood and therefore unreliable. Typical CSF changes can also be absent if patients are already receiving antibiotic treatment for other infections such as pneumonia. In our study, only cell count showed a significant BM-related increase, but cannot reliably be evaluated because diagnosis of BM was based on that parameter in some patients. In gen-

Blood glucose in patients with aneurysmal subarachnoid haemorrhage (SAH) and bacterial meningitis. Individual courses of blood glucose in patients with SAH and bacterial meningitis. Concentrations on three days before diagnosis of meningitis and on the day of diagnosis are presented for those patients with a complete dataset for that period. Each line represents one individual patient. P values were calculated using Wilcoxon signed-rank test.

Figure 2

(a) Cerebral extracellular glucose and lactate/glucose (L/G) ratio in patients with SAH and bacterial meningitis. Daily median microdialysate concentrations on three days before diagnosis of meningitis and on the day of diagnosis are presented for those patients with a complete dataset for that period. Each line represents one individual patient. P values were calculated using Wilcoxon signed-rank test.

(b) Cerebral extracellular glucose and lactate/glucose (L/G) ratio in patients with SAH and bacterial meningitis. Daily median microdialysate concentrations on three days before diagnosis of meningitis and on the day of diagnosis are presented for those patients with a complete dataset for that period. Each line represents one individual patient. P values were calculated using Wilcoxon signed-rank test.

Figure 3

Blood glucose in patients with aneurysmal subarachnoid haemorrhage (SAH) and bacterial meningitis. Individual courses of blood glucose in patients with SAH and bacterial meningitis. Concentrations on three days before diagnosis of meningitis and on the day of diagnosis are presented for those patients with a complete dataset for that period. Each line represents one individual patient. P values were calculated using Wilcoxon signed-rank test.
eral, CSF leucocyte count after SAH is often altered by blood cells and can even be impossible to evaluate in extremely bloody CSF. The insufficiency of CSF analysis for diagnosis of BM in these patients was strikingly demonstrated by Schade and colleagues [3]. In a study investigating the value of routine CSF analysis for diagnosis of BM in patients with external drains, it was not possible to establish a cutoff value with a sensitivity and specificity of at least 60% for any of the parameters of leucocyte count, protein, glucose and CSF/blood glucose ratio. Gram stain of CSF samples reached a specificity of 99.9%, but sensitivity was as low as 39.8% [3]. Still, routine CSF analysis remains recommended in patients with external drains, but these data clearly illustrate the need for additional tools to guide the diagnosis of bacterial meningitis in patients with SAH.

**Changes in MD parameters during bacterial meningitis**

MD is used for monitoring cerebral metabolism in patients with SAH. Among others, glucose and lactate levels are usually assessed. The CSF concentrations of these markers are routinely used for diagnosis of BM, so their cerebral extracellular concentrations can also be expected to indicate BM-related changes. So far, MD data in meningitis are only available from experimental studies carried out mainly for measurement of drug penetration or pathophysiology of BM-related neuronal injury, and from two case reports in humans.

An experimental study in rabbits with pneumococcal meningitis revealed a cerebral increase in lactate and a decrease in glucose, and the authors conclude that BM leads to anaerobic glycolysis with increased lactate production within the brain [10]. A trial evaluating the permeability of antibiotics across the blood-brain barrier showed an increase in cerebral lactate and glutamate, and a slight increase in glycerol towards the end of the 24-hour observation period. Extracellular glucose was not measured in that study [27]. In an investigation of MD concentrations of several amino acids in a rabbit model of pneumococcal meningitis, glutamate was greatly elevated and was interpreted as an indicator that excitotoxic neuronal injury may play a role in BM [28]. In rabbits undergoing Escherichia coli meningitis, significant but late elevations in the excitatory amino acids aspartate and glutamate as well as in the inhibitory neurotransmitters γ-amino butyric acid and taurine were...
observed, which the authors assume – in contrast to the preceding study – to be caused by cerebral ischaemia because of septic shock rather than the meningitis itself [29].

The available patient case reports focus on pathophysiological disturbances in the course of BM, not on early metabolic changes that could be used to guide diagnosis. In a patient with BM after a severe head injury, cerebral glucose decreased below the detection limit, combined with moderately high lactate levels and a marked increase in glutamate and pyruvate [8]. In another case of MD monitoring during meningoencephalitis, L/P ratio and glycerol were reported to remain stable, the other parameters were not mentioned [9].

Considering these results, a reduction in cerebral glucose and an increase in lactate are most likely to be expected during BM, eventually combined with an increase in glutamate. In the present study, glucose decreased markedly in the days before diagnosis of BM, but no significant changes in lactate, pyruvate or L/P ratio were noted. This might be due to the fact that the lactate levels and the L/P ratio take different courses according to the patient’s clinical group (presence or absence of acute/delayed neurological deficits), so BM-related changes might have been obliterated by these alterations [4]. A significant change in glutamate was also not noted. A possible meningitis-related increase might have been masked by the continuous glutamate decrease, which is part of the spontaneous course after SAH in the absence of ischaemia, or have been oppressed by antibiotic treatment.

In our study, a decrease in cerebral glucose of 1 mmol/L had a high sensitivity (92%) but low specificity (50%) for the diagnosis of BM. Together with the presence of fever of 38°C or above, acceptable sensitivity (69%) and specificity (80%) were reached. This reduction in sensitivity when temperature was included as a diagnostic factor can be explained by the absence of fever in some patients with possible impaired temperature regulation after SAH. As mentioned before, none of the standard CSF parameters used for the diagnosis of BM achieves a sensitivity or specificity of at least 60% in patients with external ventricular drains [3]. Considering this, cerebral MD might prove to be a useful tool not only to give pathophysiological insight in meningitis-related changes in brain metabolism, but also to facilitate diagnosis of BM in patients undergoing MD monitoring for the detection of symptomatic vasospasm, and thereby allowing earlier diagnosis and treatment to improve outcome. However, its diagnostic value will have to be confirmed prospectively in a larger patient population.

Limitations of this study
There are several limitations of this study. Above all, the retrospective design did not allow exact definitions of the criteria for diagnosis of BM, and some patients might have been missed. No other infections simultaneously to BM were registered in the patient records. However, retrospectively, it cannot be excluded that another infection was present in some cases. Neither can the diagnostic value of the CSF cell count for BM be evaluated in this study, because diagnosis of meningitis had in some patients been based on this parameter which would bias the statistical analysis. Furthermore, MD is a regional method with the volume of brain tissue monitored by the catheter covering only a few millimeters from the membrane, and metabolic processes in the brain tissue affected by SAH might not always be representative for the whole brain. Finally, in spite of the large number of patients, only a few individuals sustained BM during the period of MD monitoring. Therefore, this work should be considered a pilot study, and

| Glucose decrease ≥ 1 mmol/L | Body temperature ≥ 38°C | Glucose decrease ≥ 1 mmol/L AND body temperature ≥ 38°C |
|-----------------------------|------------------------|--------------------------------------------------------|
| Sensitivity                 | 92%                    | 83%                                                    | 69%                                          |
| Specificity                 | 50%                    | 60%                                                    | 80%                                          |
| Positive predictive value   | 20.1%                  | 22.1%                                                  | 32.0%                                        |
| Negative predictive value   | 97.9%                  | 96.6%                                                  | 95.0%                                        |

The results are displayed for a decrease in cerebral extracellular glucose of ≥ 1 mmol/L over variable time spans within the observation period, and for presence of fever ≥ 38°C. Positive and negative predictive values were calculated for a prevalence of meningitis of 12%, as found in the present study.
the reliability of cerebral metabolic changes measured by MD for diagnosis or prediction of BM in patients with SAH will have to be confirmed prospectively in a substantially larger study population. Nevertheless, this is the first study to our knowledge evaluating cerebral metabolic changes during BM in humans.

Conclusions
BM is a relevant complication in patients with SAH, and ICU stay was prolonged by an average of 5.6 days in patients with SAH and BM. The validity of clinical signs and routine CSF analysis for the diagnosis of BM in patients with SAH is limited.

A decrease in MD glucose combined with the presence of fever indicated BM with acceptable sensitivity and specificity, while CSF chemistry including leucocyte count, protein and glucose failed to indicate BM. In patients with SAH where CSF cell count is not available or helpful, MD changes may serve as an adjunct criterion for early diagnosis of BM. The power of this study is limited because of the small patient number and the retrospective design, so the results will have to be confirmed in a larger, prospective study.

Key messages
• BM occurred in 12% of patients with SAH
• In patients with SAH developing BM, ICU stay was prolonged by an average of 5.6 days
• CSF chemistry failed to indicate BM after SAH
• A decrease in MD glucose levels by 1 mmol/L, combined with fever of 38°C or above indicated BM with a sensitivity of 69% and a specificity of 80%

Competing interests
The authors declare that they have no competing interests.

Authors’ contributions
FS participated in the design of the study and performed part of the statistical analysis, created the tables and figures and drafted the manuscript. He also managed the MD monitoring and collected the MD and blood samples from some of the patients and compiled the data from the patients’ files. PF performed part of the statistical analysis. AN collected the MD and blood samples from some of the patients and compiled the data from the patients’ files. PV supervised MD monitoring and revised the manuscript for important intellectual content. AS conceived of the study and, as the project leader, was responsible for the design, coordination and data interpretation and participated in drafting the manuscript.

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