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Delayed Cerebral Vasculopathy in Pneumococcal Meningitis: Epidemiology and Clinical Outcome. A Cohort Study

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ABSTRACT

Background: To describe the prevalence, clinical characteristics, impact of systemic steroids exposure and outcomes of delayed cerebral vasculopathy (DCV) in a cohort of adult patients with pneumococcal meningitis (PM).
Methods: Observational retrospective multicenter study including all episodes of PM from January 2002 to December 2015. DCV was defined as proven/probable/possible based upon clinical criteria and pathological-radiological findings. DCV-patients and non-DCV-patients were compared by univariate analysis.
Results: 162 PM episodes were included. Seventeen (10.5%) DCV-patients were identified (15 possible, 2 probable). At admission, DCV-patients had a longer duration of symptoms (>2 days in 58% vs. 25.5% (p 0.04)), more coma (52.9% vs. 21.4% (p 0.03)), lower median CSF WBC-count (243 cells/uL vs. 2673 cells/uL (p 0.001)) and a higher proportion of positive CSF Gram stain (94.1% vs. 71% (p 0.07)). Median length of stay was 49 vs. 15 days (p 0.001), ICU admission was 85.7% vs. 49.5% (p 0.01) and unfavorable outcome was found in 70.6% vs. 23.8% (p 0.001). DCV appeared 1-8 days after having completed adjunctive dexamethasone treatment (median 2,5, IQR = 1.5-5).
Conclusions: One tenth of the PM developed DCV. DCV-patients had a longer duration of illness, were more severely ill, had a higher bacterial load at admission and had a more complicated course. Less than one third of cases recovered without disabilities. The role of corticosteroids in DCV remains to be established.
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1. Introduction

Streptococcus pneumoniae (Sp) is the predominant causative pathogen of community-acquired bacterial meningitis (C-ABM) in adults, causing up to 53% of cases (van de Beek et al., 2016). Pneumococcal meningitis (PM) is associated with a high mortality rate (18-26%) and a high rate of neurological sequelae (20-37%) in surviving patients (van de Beek et al., 2006), (Lucas et al., 2016).

Cerebrovascular complications are associated with poor prognosis and occur frequently during PM, including arterial ischemic stroke (14 - 25%), cerebral venous thrombosis (1 - 9%), intracranial hemorrhage (1 - 5%) and cerebral vasculitis (van de Beek et al., 2016), (Schut et al., 2012), (Vergouwen et al., 2010). After the

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widespread implementation of adjunctive dexamethasone (aDXM) in adults with PM, a rare cerebrovascular complication characterized by an initial good recovery followed by sudden deterioration several days after presentation has been described. Some cases of delayed cerebral vasculopathy (DCV) or thrombosis have been reported (Schut et al., 2009), (Lucas et al., 2013), (Wittebole et al., 2016), (Gallegos et al., 2018), but studies on its incidence, clinical spectrum, prognosis and impact of the use of aDXM are scarce.

The aims of the present study were to identify the prevalence of DCV in a cohort of adult patients with PM, and to describe the clinical course, the impact of dexamethasone exposure and outcomes.

2. Methods

2.1. Study design, setting and patients

A retrospective observational multicenter study was carried out in two acute-care teaching hospitals in Barcelona, Spain, which are both Neurosurgery referral centers. Hospital Universitari de Bellvitge (HUB) is a 700-bed teaching hospital (mean annual admission of 34,000 patients) and the Hospital Universitari Mútua Terrassa (HUMT), a 400-bed teaching hospital (mean annual admission of 24,000 patients).

All episodes of PM in adults ($\geq$ 16 years old) were prospectively recorded in a database since 1977 in HUB or identified through the Microbiology Laboratory records in HUMT. All PM cases identified from January 2002 to December 2015 were included and retrospectively reviewed.

The following variables were collected: Demographic and clinical characteristics, radiological, laboratory and clinical findings at admission; antimicrobial treatment and aDXM (duration and doses); evolution and outcomes. Data were collected from the medical charts and electronic medical records of both hospitals.

STROBE recommendations (Vandenbroucke et al., 2014) were followed to strengthen the reporting of the study results (supplementary material, Table S1).

2.2. Definitions

PM was diagnosed in patients with compatible clinical findings suggestive of meningitis and 1 or more of the following: positive CSF culture for Sp, positive CSF Gram stain for Sp, positive CSF immunochromatographic antigen test for Sp, positive blood culture for Sp and CSF pleocytosis ($\geq$ 5cells/mm3).

DCV was defined by a multidisciplinary team based upon clinical criteria and pathological-radiological findings (Table 1) (Calabrese and Mallek, 1988), (Ehsan et al., 1995), (Zuber et al., 1999). We defined the clinical criteria of DCV as: (a) clinical worsening after 72 hours of admission with a new onset of fever and/or neurological symptoms without an alternative diagnosis, and/or (b) lack of improvement after 72 h of adequate antimicrobial and corticosteroids treatment without an alternative diagnosis. The presence of seizures, focal neurologic deficits, a fall in the Glasgow coma scale (GCS) or death in the first 72 h were not considered DCV clinical criteria. When clinical criteria were met, DCV was classified according to the pathological and radiological findings (Table 1) in proven, probable or possible. (i) Proven: compatible biopsy or autopsy, (ii) probable: compatible arteriography, angiography-CT/MRI, (iii) possible: compatible CT/MRI.

Immunosuppression was defined by the presence of at least one of the following: infection with the human immunodeficiency virus, chronic corticosteroid therapy, and use of immunosuppressive agents or biological drugs. Corticosteroid therapy was defined as > = 5 mg/24 hours of prednisone or an equivalent dose of another corticosteroid. Comorbidities considered included diabetes mellitus, hepatic cirrhosis, asplenia, and solid and haematologic neoplasm.

Time to admission was defined as the time from onset of symptoms to the first dose of appropriate antibiotic therapy. Patients with duration of illness at admission longer than 2 days were defined as having late presentation. A Glasgow Coma Score (GCS) < 14 was defined as altered mental status, GCS < 8 was defined as coma. Cranial computed tomography (CT) was not routinely performed at admission. Cranial CT or MRI during admission was performed according to the individual criteria of each physician at charge.

The lack of improvement after 72 h of appropriate treatment and the presence of clinical worsening after an improvement were defined as a clinical complication. Recurrent fever was defined as fever reappearing after at least 1 afebrile day (Weisfelt et al., 2006).

Outcome and sequelae were graded with the Glasgow Outcome Scale (GOS) (Jennett et al., 1976), a scale with scores varying from one to five: 1 = death; 2 = vegetative state; 3 = major disability;

Table 1
Pathological and radiological findings established to classify DCV

PATHOLOGICAL-RADIOLOGICAL FINDINGS		
POSSIBLE	Cranial CT	Multiple infarctions in different vascular territories Bilateral infarctions Lesions in different state of evolution Multiple hemorrhages (parenchyma and/or subarachnoid) Bilateral hemorrhages Coexisting hemorrhagic and ischemic lesions Blunt lesions
	Cranial MRI	Previous CT findings (more sensitive) + : Punctate white matter hyperintense lesions in T2 and FLAIR Tumor-like lesions
PROBABLE	Angiography-CT/Angiography-MRI or Arteriography	Stenosis or ectasia Focal dilatations Vessel irregularities Multiple occlusions with sudden stops Effusion of vascular contour Alteration of circulation time
PROVEN	Compatible biopsy or autopsy	

* only one criterion is defining in each section.
DCV: Delayed Cerebrovascular Vasculopathy, CT: Computerized tomography, MRI: Magnetic resonance imaging.
(Calabrese and Mallek, 1988), (Ehsan et al., 1995), (Zuber et al., 1999).

4 = moderate disability; 5 = good recovery, no disability. A favorable outcome was defined as a score of 5 and an unfavorable outcome as a score of 1–4.

2.3. Treatment

Empirical treatment was considered adequate if the antibiotic used was active in vitro against the strain isolated. Definitive therapy was penicillin or cefotaxime/ceftriaxone at meningeal doses or vancomycin, in all cases following the hospital guidelines. aDXM was defined as the administration of dexamethasone at admission, before or with the first dose of antibiotic therapy.

In HUB, all patients with suspected PM have been treated since 1987 with aDXM 4 mg/6 h for 48 hours, eight doses in total, beginning 10–15 minutes before antibiotic therapy with a doubled first dose.

In HUMT, aDXM 10 mg/6 h for 96 h, beginning 10–15 min before antibiotic therapy has been administered on suspicion of C-ABM ever since the publication of the results of a European controlled trial in C-ABM (de Gans and van de Beek, 2002) in 2002.

2.4. Statistical analysis

All statistical analyses were performed using SPSS, version 15.0 (SPSS Inc., Chicago, Illinois). Categorical variables are presented using counts and percentages and continuous variables as means and standard deviation (SD) or medians and interquartile range (IQR).

Table 2
General characteristics of 162 patients with PM, and comparison between DCV-patients and non-DCV-patients.

Variables	PM patients N = 162, N (%)	DCV patients N = 17, N (%)	non-DCV patients N = 145, N (%)	*p*
Age (years), median (IQR)	62 (49-71)	58 (45 – 72)	62 (49 -71)	0.81
Gender, male	88 (54.3)	10 (56.8)	78 (53.8)	0.69
Recurrent meningitis	17 (10.5)	4 (23.5)	13 (9)	0.08
Source of infection *				0.32
- No identified source	27 (16.7)	4 (23.5)	23 (15.9)	
- Probable CSF leaks	12 (7.4)	3 (17.6)	9 (6.2)	
- Proven CSF leaks	24(14.8)	2 (11.8)	22 (15.2)	
- Chronic sinusitis	6 (3.7)	2 (11.8)	4 (2.8)	
- Acute sinusitis	8 (4.9)	2 (11.8)	6 (4.1)	
- Acute otitis	74 (45.7)	3 (17.6)	71 (49)	
- Pneumonia	8 (4.9)	1 (5.9)	7 (4.8)	
- Others	9 (5.6)	1 (5.9)	8 (5.5)	
Comorbid conditions				
Diabetes mellitus	31/125 (24.8)	2/14 (14.3)	29/111 (26.1)	0.51
Chronic liver disease	11/125 (8.8)	1/14 (7.1)	10/111 (9)	1
Splenectomy	5/125 (4)	3/14 (21.4)	2/111 (1.8)	0.01
Haematologic neoplasia	17/125 (13.6)	3/14 (21.4)	14/111 (12.6)	0.41
Solid neoplasia	9/125 (7.2)	0	9/111 (8.1)	0.6
Immunosuppression	13 (8)	3 (17.6)	10 (6.9)	0.12
Clinical features on presentation				
Fever >38 °C	121 (74.7)	10 (58.8)	111 (76.6)	0.11
Headache	115 (71)	10 (58.8)	105 (72.4)	0.24
Neck stiffness	109 (67.3)	7 (41.2)	102 (70.3)	0.02
Vomiting	82 (50.6)	8 (47.1)	74 (51)	0.76
Duration of symptoms				
-<12 hours	42 (26.1)	3 (17.6)	39 (26.8)	0.76
- 12-48 hours	72 (44.7)	4 (23.5)	68 (46.9)	0.12
->2 days	47 (29.2)	10 (58.8)	37 (25.7)	0.004
Score on Glasgow Coma Scale				
-<14 (altered mental status)	95 (58.6)	7 (41.2)	88 (60.7)	0.47
-<8 (coma)	40 (24.7)	9 (52.9)	31 (21.4)	0.03
Cranial nerve palsies	15 (9.5)	2 (11.8)	13 (9.2)	0.67
Hemiparesia	14 (8.7)	2 (11.8)	12 (8.3)	0.65
Convulsion	23 (14.4)	1 (5.9)	22 (15.4)	0.47
Microbiological and biochemical findings at admission				
Positive Gram stain	119 (73.5)	16 (94.1)	103 (71)	0.04
Positive CSF culture	120 (74.1)	16 (94.1)	104 (71.7)	0.07
Positive blood cultures	119 (73.5)	15 (88.2)	104 (71.7)	0.24
CSF characteristics				
WBC count (cells/uL), median (IQR)	2500 (576-5650)	243 (97.5-611)	2673 (810-6000)	0.001
Neutrophil (%), median (IQR)	93 (85.5-96.5)	89 (75-92)	93 (86-97)	0.15
CSF: blood glucose ratio <0.4	137/158 (86.5)	15/16 (93.8)	122/142 (85.9)	0.7
Protein (g/L)				0.18
<1	10/155 (6.5)	0	10 (6.9)	
1-5	77/155 (49.7)	7 (41.2)	70 (48.3)	
5-10	55/155 (35.5)	8 (47.1)	47 (32.4)	
>10	13/155 (8.4)	0	13 (9)	
Treatment at admission				
Appropiate empirical antimicrobial (AM) treatment	145/147 (98.6)	15/16 (93.8)	130/131 (99.2)	0.21
Directed therapy with cephalosporins or penicillin at high doses	154/156 (98.7)	17/17 (100)	137/139 (98.6)	1
AM duration (days), median (IQR)	10 (10-14)	15 (10-22)	10 (10-12)	0.025
Adjunctive dexamethasone (DXM)	154/158 (97.5)	15/16 (93.8)	139/142 (97.9)	0.35
DXM duration (days), median (IQR)	3 (2-5)	5 (4-8)	2 (2-4)	0.26

* Numbers do not add up to total because of the presence of multiple sources in several patients.PM: Pneumococcal meningitis, DCV: Delayed Cerebral Vasculopathy, IQR: Interquartil range, CSF: Cerebrospinal fluid, WBC: White blood cells, AM: antimicrobial, DXM: dexamethasone.

Comparative analyses were performed with the Chi-square test or Fisher exact test for categorical variables and t-test or Mann-Whitney test for continuous variables, when appropriate. Differences were considered statistically significant at the two-sided $p < 0.05$ level.

3. Results

3.1. Baseline characteristics

A total of 162 episodes of PM were identified during the study period, 128 in HUB and 34 in HUMT. Seventeen (10.5%) cases of DCV were identified: 15 (9.3%) were classified as possible and 2 (1.2%) as probable.

Table 2 shows the epidemiological and clinical characteristics at admission and the laboratory findings of the 162 episodes of PM, as well as the comparison between patients with DCV (DCV-patients) and those without it (non-DCV-patients).

The serotypes identified in both groups were similar.

Cranial CT at admission was performed in 138 (85.2%) episodes (Table 3). During admission Cranial CT or MRI was performed when intracranial abnormalities were suspected, in 41/47 episodes (87.2%). Arteriography or angiography-CT/MRI was carried out in 6/47 cases (12.8%) and 2 of the findings showed compatibility with DCV. A cerebral biopsy was performed to a patient with clinical and radiological suspicion of DCV, but DCV could not be confirmed.

3.2. Treatment

Table 2 shows the characteristics of the empirical and directed antimicrobial treatment and the aDXM treatment. Two cases received directed therapy with vancomycin: one due to penicillin allergy and beta-lactam resistance, and the other one due to beta-lactam resistance (penicillin MIC 2 μg/mL, cefotaxime MIC 1 μg/mL for both cases). 97.5% of cases received aDXM treatment during a median of 3 days (IQR 2-5), without differences between DCV-patients and non-DCV-patients.

3.3. Evolution and outcomes

Table 4 shows the evolution and outcomes in the entire cohort and the comparison between DCV-patients and non-DCV-patients. There were no meningitis relapses. Patients were followed up 90 days after discharge (median, IQR 39 - 339).

3.4. DCV patients

DCV appeared within 4-27 days after admission (median = 7, IQR = 4.5-8). Referral data from one of the patients was missing. At the DCV presentation, 3/16 patients (18.8%) were not receiving antibiotic and in 12/16 (75%) patients aDXM was stopped in the previous 1-8 days (median = 2.5, IQR = 1.5–5). Targeted treatment either started or modified for DCV consisted in: (1) antimicrobials in 9/16 patients (56.3%) during 3-44 days (median = 16, IQR = 12-19), (2) dexamethasone in 14/16 patients (87.5%) during 12-180 days (median = 39.5, IQR = 16-97), with median doses the first 24 hours of 16 mg (IQR 9.5-24). Five patients (29.4%) recovered showing no disability, 2 of them had not been treated with dexamethasone, 10 (58.8%) recovered with major or moderate disability, and 2 patients (11.8%) died, both under dexamethasone treatment. Description of DCV-cases is shown in Table 5.

4. Discussion

This is the largest cohort of DCV in adults with PM published to date, and the first study that evaluates its clinical characteristics, outcome and relationship with aDXM. Since the use of aDXM was routinely standardized, some cases of cerebral vasculitis or delayed cerebral thrombosis occurring after an initial clinical improvement of the PM have been described (Schut et al., 2009), (Lucas et al., 2013), (Wittebole et al., 2016), (Gallegos et al., 2018), (Lefebvre et al., 2007), (Pugin et al., 2006), (Katchanov et al., 2010), (Rice et al., 2012), (Regaieg et al., 2016), (Ribeiro et al., 2013), (Darling et al., 2012). However, neither this clinical entity nor the role of aDXM or treatment with corticosteroids has been defined.

Our study shows that DCV is not uncommon; more than one tenth of adults with PM showed clinical worsening after systemic steroids discontinuation, developing a probable or possible DCV.

There were no differences in demographic characteristics among DCV-patients and non-DCV-patients. No populations at risk of developing DCV could be identified due to the small sample size, but in the DCV-group there were more underlying conditions that may predispose either to develop PM (splenectomy (21.4%) and recurrent meningitis (23.5%)) or to orchestrate an inadequate immune response (haematologic neoplasia (21.4%) and immunosuppression (17.6%)). Remarkably, there were less DCV-cases when the source of infection was an acute otitis. There were no more pathological findings in CT at admission, showing that DCV appears later in the course of the disease.

Table 4
Evolution and outcome in patients with PM, and comparison between DCV-patients and non-DCV-patients

Variables	PM patients N = 162, N (%)	DCV patients N = 17, n (%)	Non-DCV patients N = 145, n (%)	*p*
Length of hospital stay, median (IQR), days	16 (12 – 26)	49 (31 - 62)	15 (11 - 23)	0.001
Fever recurrence	47/153 (30.7)	11/16 (68.8)	36/137 (26.3)	0.001
Neurological complication*:	41 (25.3)	17 (100)	24 (16.6)	0.001
Stroke	19 (11.7)	17 (100)	3 (2.1)	0.001
Brain abscess	6 (3.7)	1 (5.9)	5 (3.4)	0.49
Venous Trombosis	1 (0.62)	0	1 (0.69)	1
Subdural empyema	5 (3.1)	1 (5.9)	4 (2.8)	0.43
Others [&]	12 (7.4)	0	12 (8.3)	0.22
Intensive Care Unit	80/153 (52.3)	12/14 (85.7)	68/139 (49.5)	0.010
Mechanical Ventilation	66/153 (43.1)	10/13 (76.9)	56/140 (40)	0.017
Glasgow Outcome Score				
- Unfavorable outcome	42/143 (29.4)	12/17 (70.6)	30/126 (23.8)	0.001
- Favorable outcome	101/143 (70.6)	5/17 (29.4)	96/126 (76.2)	0.001
Mortality	19 (11.8)	2 (11.8)	17 (11.8)	1

PM: Pneumococcal Meningitis, DCV: Delayed Cerebrovascular Vasculopathy, IQR: Interquartil range.
* Numbers do not add up to total because of the presence of multiple complications in several patients.
& Seizures 3 (12%), neuritis III cranial nerve 3 (12%), exitus due to meningitis 4 (16%), disseminated acute encephalomyelitis 1 (4%), Raeder paratrigeminal syndrome 1 (4%).

Table 5
Description of DCV patients

Case	Sex/Age	Serotype[&]	Comorbidities	Days to DCV[a]	Clinical features[b]	Previous treatment[c]	DCV treatment[d]	Radiological findings DCV	Outcome (GOS*)
1	Male/37	23A	SP, LC, IS	4	RF	ATB 4d, aDXM 4d	ATB 15d	CT, MRI	5
2	Male/72	4	–	5	RF, FNA, AMS	ATB 5d, aDXM 5d	ATB 9d, DXM 13d	CT, MRI	3
3	Male/39	19F	–	12	PF, FNA	ATB 11d, aDXM 6d	ATB 44d, DXM 77d	CT	4
4	Male/45	9V	–	4	C, AMS	ATB 4d, aDXM 2d	ATB 6d, DXM 16d	CT, MRI	4
5	Male/59	19[a]	–	12	RF, FNA, Cv	ATB 11d, aDXM 12d	ATB 9d, DXM 23d	MRI	5
6	Female/57	NA	–	7	RF, FNA, AMS	ATB 7d, aDXM 2d	ATB 11d, DXM 15d	CT, MRI	3
7	Female/37	15C	–	4	AMS	ATB 4d, aDXM 2d	ATB 11d, DXM 56d	MRI	4
8	Female/69	–	–	–	–			MRI	3
9	Male/53	10[a]	SP, HN, IS	4	AMS	ATB 4d, aDXM 3d	ATB 6d, DXM 63	CT, MRI	1
10	Female/73	19[a]	–	6	RF	ATB 6d, aDXM 4d	ATB 8d, DXM 17d	MRI	5
11	Male/50	12F	SP	8	RF, Cv	ATB 8d, aDXM 4d	ATB 16d, DXM 180d	CT	4
12	Male/63	1	HN	10	FNA, AMS	ATB 10d, aDXM 7d	ATB4d, DXM 97d	MRI	5
13	Female/75	3	DM	6	RF, FNA, AMS	ATB 6d, aDXM 5d	ATB 12d, DXM 8d	MRI	1
14	Female/36	23A	HN, IS	27	RF, FNA, Cv	ATB 23d, aDXM 27d	ATB 3d, DXM 180d	MRI, angio-MRI	3
15	Female/87	3	–	7	C, FNA, Cv	ATB 7d	ATB 19d, DXM 103d	MRI, angio-MRI	4
16	Male/74	16F	DM	7	RF, AMS	ATB 7d, aDXM 6d	ATB 3d, DXM 13d	MRI	4
17	Male/65	13	–	8	PF	ATB 8d, aDXM 3d	ATB 11d	MRI	5

DCV Delayed Cerebral Vasculopathy, DM diabetes mellitus, SP splenectomy, LC liver cirrosis, HN haematologic neoplasia, SN solid neoplasia, IS immunossuppresion, PF persistent fever, RF recurrent fever, C cephalea, FNA focal neurological abnomalities, Cv convulsion, AMS altered mental state, ATB antibiotic, aDXM adjunctive dexamethasone, DXM dexamethasone (or equivalent treatment with other corticosteroid), CT cranial computed tomography, MRI cranial magnetic resonance imaging, d days.
[&] Serotyping was performed by Quellung reaction at the Spanish Reference Laboratory.
[a] Days from admission to DCV.
[b] Clinical features at presentation of DCV.
[c] Treatment received for pneumococcal meningits until DCV.
[d] Treatment started or continued for DCV.
* Glasgow Outcome Scale (GOS): 1 = death; 2 = vegetative state; 3 = major diability; 4 = moderate disability; 5 = good recovery, no disability.

DCV-patients had a longer duration of symptoms and they were more severely ill at admission as measured by the GSC. A decreased level of consciousness at admission has been previously described as a factor predicting the development of cerebral infarction (Schut et al., 2012), (Katchanov et al., 2010) and unfavorable outcome (Weisfelt et al., 2006), (Kastenbauer and Pfister, 2003).

Regarding CSF characteristics, a lower median of WBC count (243 vs. 2673/mm3) and a higher proportion of positive Gram stains (94.1% vs. 71%) and culture (94.1% vs. 71.7%) were observed in DCV-patients. As previously described, a low CSF leucocyte response has been associated with immunodeficiency, high bacterial growth in CSF, development of ischemic cerebrovascular complications and with unfavorable outcome (Weisfelt et al., 2006), (Katchanov et al., 2010), (Kastenbauer and Pfister, 2003). This lower WBC count and the higher proportion of positive Gram stain and culture in CSF could suggest a milder inflammatory reaction and a higher bacterial load.

Cranial CT/MRI was performed when neurological complications were suspected. However, arteriography or angiography-CT/MRI were only performed in 12.8% of cases and only one biopsy was done. Consequently, 88.2% of DCV-cases were classified as possible, 11.8% as probable, and there were no proven cases. A higher clinical suspicion could have improved the diagnostic yield. In our opinion, clinical worsening without an alternative diagnosis after having stopped dexamethasone, should prompt the performance of an angio-CT/MRI.

DCV-patients experienced a more complicated course, as evidenced by a longer hospital stay, greater need for ICU admission and mechanical ventilation. They had more sequelae as measured by the GOS, and showed a 70.6% of unfavorable outcome. Surprisingly, there were no differences in mortality, perhaps attributable to the small sample size and the low fatality rate of our cohort.

Since 2002 aDXM is currently routinely used in the treatment of adults with PM after evidence from previous studies showing that corticosteroids reduced mortality in PM in high-income countries (de Gans and van de Beek, 2002), (Brouwer et al., 2015).

Little is known about the current prevalence of DCV in PM, since most reports on cerebrovascular complications described cohorts older than 2002 (Schut et al., 2012), (Vergouwen et al., 2010), (Kastenbauer and Pfister, 2003), before the routine use of aDXM. Some papers published later do not show a clear correlation between the use of aDXM and the development of cerebrovascular complications (Katchanov et al., 2010), (Bodilsen et al., 2014) or they do not make reference to the use of dexamethasone (Mook-Kanamori et al., 2012). Therefore, data on the long-term effect of dexamethasone in PM are lacking and information on the impact of the use of dexamethasone on cerebrovascular complications is scarce.

In 2009, Schut et al reported 6 patients with a devastating delayed vasculopathy complicating C-ABM after dexamethasone withdrawal (Schut et al., 2009). They described this new entity as delayed cerebral thrombosis (DCT) because they found an arterial thrombosis in one patient autopsy, but no evidence of vasculitis. Since then, DCT has been reported in 20 patients, with a prevalence of 1 - 4.1% (Lucas et al., 2013), (Wittebole et al., 2016), (Gallegos et al., 2018). On the other hand, some cases with a delayed clinical worsening related to the presence of cerebral vasculitis have also been published (Lefebvre et al., 2007), (Pugin et al., 2006), (Rice et al., 2012), (Regaieg et al., 2016). However, the pathological substrate of both thrombosis or vasculitis has not been consistently demonstrated.

In a recent autopsy study from the Dutch Meningitis Cohort, the authors found inflammation in the meninges and blood vessels with extensive infarction and thrombosis. However, there were no differences between patients with delayed clinical worsening and those without it (Engelen-Lee et al., 2018). Therefore, it seems that DCV is a clinical entity that can be caused by different vascular complications like thrombosis, vasculitis, disseminated intravascular coagulation, vasospasm or rebound effect of the primary inflammatory response after the withdrawal of steroids.

In this sense, some authors have suggested a gradual steroid withdrawal rather than the abruptly terminated 4-day course currently advocated, or a longer treatment with progressive tapering (Lefebvre et al., 2007), (Rice et al., 2012) in order to avoid a "rebound effect" secondary to stopping corticosteroid therapy. Recently, a retrospective study investigating the prevalence of DCV in patients with C-ABM showed that aDXM was more likely given to DCV-patients (100% (5/5) vs 37.5% (43/115) in non-DCV-patients) (Gallegos et al., 2018). However, the results must be interpreted with caution, as they only had 5 DCV-patients and the proportion of patients treated with aDXM in the whole cohort was low (40%). In our study, an association with aDXM was difficult to prove due to the high proportion of compliance with steroids (97.5%).

No randomized clinical trials addressing the benefits of different timings of corticosteroid therapy have been performed in adults. In our study, patients received a shorter aDXM treatment than the recommended one in guidelines, with a median duration of 2 days. Despite receiving a lower dose of corticosteroids, the rate of neurological complications has been 25.3% and mortality rate 11.8%, less than the figures reported in recent literature (Engelen-Lee et al., 2016). This dosage of aDXM has previously shown to be a protective factor in elderly patients with PM (Cabellos et al., 2009). Remarkably, the proportion of DCV was higher in HUMT (23.5% vs. 7.03%, p 0.005), where corticosteroids were prescribed as recommended in guidelines.

There is no evidence about who would benefit from corticosteroids reintroduction after worsening. In our study, dexamethasone was reintroduced as DCV-treatment in 87.5% of patients with heterogenous results.

Our study has some strengths: it is the largest cohort of DCV in adults published to date and shows a higher prevalence (10.5%). It represents a very homogeneous group: aDXM and appropriate empirical antimicrobial therapy were administered to most of the cohort. Clinical characteristics, outcome and the role of aDXM have been thoroughly investigated and described. Finally, an effort to define the diagnostic criteria of DCV by a multidisciplinary team has been attempted for the first time.

Main limitations of our study are: (a) it is a retrospective observational study; (b) CT was not performed systematically at admission or whenever patients had neurological complications, and this could have led to an underestimation of the prevalence of DCV. The poor performance of angiographic imaging may have underdiagnosed and misclassified DCV-cases. (c) The sample size did not allow us to identify strong correlations. Finally, our study was conducted in a specific geographical area, and the results cannot be extrapolated to other settings.

The prevalence of delayed cerebral vasculopathy is relevant, with more than one tenth of the PM developing a probable or possible DCV. Patients that developed DCV presented a more severe illness, lower inflammatory CSF response and higher bacterial load at admission. DCV is a severe neurological complication, as reflected by a longer hospital stay, greater need for ICU admission and more sequelae, with more than two thirds of unfavorable outcomes. The role of corticosteroids in DCV and their dosage remain to be established.

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Conflict of interest

E. C. has accepted grants, speaking engagements and conference invitations from Astellas, AstraZeneca, Novartis, Pfizer and MSD. J. G. has accepted grants from Menarini and Nabriva, and speaking engagements and conference invitations from Astellas, AstraZeneca, Novartis, Pfizer, GSK, Bayer, Vifor Pharma, Cubist, Durata and Theravance. C. A. has received funding from Pfizer. All other authors: none to declare.

Ethical approval

The study was approved by the local ethics committee.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at https://doi.org/10.1016/j.ijid.2020.06.005.

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