International Journal of Pharmaceutical Science Invention
ISSN (Online): 2319 – 6718, ISSN (Print): 2319 – 670X
www.ijpsi.org Volume 5 Issue 4 ǁ July 2016 ǁ PP.01- 06

Clinical and Laboratory Prognostic Factors in Malignant form of Mediterranean Spotted Fever

Baltadzhiev I[1], Popivanova N[1], Zaprianov Z[2]
[1]*Department of Infectious Diseases, Parasitology and Tropical Medicine, Faculty of Medicine, Medical University, Plovdiv, Bulgaria;*
[2]*Department of Clinical Pathology, Faculty of Medicine, Medical University, Plovdiv, Bulgaria*

ABSTRACT: *Mediterranean spotted fever (MSF) caused by Rickettsia conorii has become a significant health risk for suffering people and international travelers. In the past, overlooked as a serious disease, at present it is known that MSF was wrongly considered a benign condition. In this report, we present a set of clinical features and laboratory parameters in 55 patients (19 fatalities and 36 survivors) with malignant forms of the disease. The purpose of the study was to outline the prognostic factors of the fatal outcome in patients with malignant MSF. Based on our data, the main prediction factors for mortality in malignant MSF patients were: advanced age, delayed hospital admission, severe concomitant diseases, and failure to start or to complete appropriate antibiotic treatment. Laboratory prognostic factors in fatalities were: leukocytosis with a marked shift to the left; extremely high serum urea and creatinine levels; low levels of fibrinogen and prolongation of thrombin time. The most frequently involved organ systems of malignant cases were: central nervous system 100%, liver 92.72%, kidneys 60%, lungs 58.18%, myocardium 30.9%, and gastrointestinal tract 23.63%. The conducted histopathological investigations revealed lethal complications: encephalitis, brain edema, acute respiratory distress syndrome, non-cardiogenic lung swelling, acute myocarditis, gastrointestinal bleeding, hemorrhagic-necrotizing pancreatitis and acute renal failure.*

Keywords: *Mediterranean spotted fever, malignant forms, prognostic factors*

I. Introduction

Mediterranean spotted fever (MSF), known as „Marseilles fever" or „Boutonneuse fever" is a rickettsial disease endemic for the countries along the Mediterranean coast (South Europe and North Africa). However, a growing number of cases are reported from Central and Eastern Europe [1, 2]. As a result of globalization and growing tourism, imported cases of MSF are reported in many non-endemic countries and regions. Molecular instruments as PCR and sequencing have identified the responsible for the disease rickettsial agent *Rickettsia conorii subsp. conorii, strain Malish Seven* [1]. The main epidemiological feature of MSF is the transmission of rickettsiae to humans in the endemic regions by the bite of the brown dog tick Rhipicephalus sanguineus during the favorable for tick's biology spring-summer season. Another important epidemiological determinant is the human contact with tick's intermediate hosts - domestic and stray dogs [3, 4]. The main clinical signs and symptoms of MSF are: skin eschar (black spot or tache noire) at the site of the tick bite, fever and flu-like manifestations as headache, adynamia, anorexia, myalgia, etc., emerging 3-5 days before the onset of papular or maculopapular rash over the trunk and extremities, involving the hands and feet.

Known in Europe since the beginning of the twentieth century, MSF has long been considered a benign disease. In the early 1980s, D.Raoult reported a patient with a fatal outcome due to MSF and used the term «malignant» for the most severe forms of the disease [5]. In 1980s and 1990s, the disease was particularly common in many European countries, and severe, "malignant" including lethal cases have been observed. The mortality rate reached 54.5% in hospitalized patients with neurological manifestations and multiorgan involvement [6]. Currently it is known that MSF is, at least as severe as Rocky Mountain spotted fever (RMSF). In Bulgaria MSF was described in 1948 and for over two decades (1948-1972) had presented as a mild to moderate disease without registered mortality [7]. Following a 20 year pause, during which the disease was considered eliminated, it reemerged in the early 1990s and rapidly affected thousands of people in the endemic regions. During this "second wave" various forms of the disease were observed, and very severe, actually "malignant" forms were reported, some of them even fatal. In one of our investigations (which included 549 patients in the largest endemic region of Bulgaria – the city of Plovdiv and the neighboring areas with a population of approximately 700 000 inhabitants), the MSF incidence rate was 11.88 per 100 000 individuals. The cases were defined as mild - 226 (41.16%), moderate - 180 (32.79%), severe - 88 (16.03%) and malignant - 55 (10.02%) [3]. The grading was based on the establishment of a set of clinical and laboratory criteria [8]. Lethality rate in all treated patients was 3.46%, and mortality in malignant forms reached 34.54%.

II. Aims & Objectives

The purpose of this study was to determine the clinical and laboratory prognostic factors contributing to the fatal outcome in patients with malignant MSF.

III. Patients and Methods

Fifty five patients (30 men and 25 women) with malignant forms of MSF were involved in the study. They were divided in two groups: Group I comprised 19 fatalities with mean age 59.55±4.09 years; Group II comprised 36 survivors with mean age 47.22±5.81 years (Mean±SEM), $p>0.05$). MSF was proven by the indirect immunofluorescent assay (IFA), with at least a fourfold increase in the antibody titer to a specific *R.conorii* antigen (IFA test *Rickettsia conori*—Spot IF, BioMerieux, Marcy L'Etoile, France). IgG titres of ≥128 and ⁄or IgM titres of >64 were considered indicative of acute infection [9]. Diagnostic laboratory confirmation by IFA was performed at the Referent Laboratory of the Military Medical Academy in Sofia, Bulgaria. In addition to the serological confirmation of MSF, our patients fulfilled the clinical and epidemiological scoring criteria for Mediterranean spotted fever diagnosis, adopted by the members of the European Network for Surveillance of Tick-Borne Diseases [9]**.**

Inclusion criteria: patients had to meet our criteria for a malignant form of MSF. The criteria have been published elsewhere [8] and are as follows: extremely severe toxic-infection syndrome, temperature ≥ 40°C, chills, severe headache, nausea, vomiting, typhoid mental condition, stupor, coma; abundant maculopapular and/or haemorrhagic rash, presence of clinically apparent lesions in more than one organ system (pneumonitis, jaundice, acute renal failure, gastrointestinal hemorrhage, myocarditis, CNS damage); platelet count of $\leq 50\times10^9$/l or $<100\times10^9$/l; serum sodium of ≤ 130 mmol/l; ALT/AST levels increased at least 5 times the baseline; hypocalcemia, hypoalbuminemia, hypoxemia. The presence of at least two clinical syndromes and two laboratory criteria of the above mentioned, defines the MSF form as malignant. The IgM titre >1:64 to *R.conorii* antigen and/or the fourfold titre elevation within 2 weeks was considered indicative of recent infection.

Exclusion criteria: patients with preceding and/or accompanying end-stage co-morbidities, which might result in, or contribute to the fatal outcome; glucose-6-phosphate dehydrogenase (G6PD) deficiency; history of treatment with antibiotics potentially active against *Rickettsia species* prior to hospitalization.

Statistics: Data were analyzed using statistical software SPSS version 15 (SPSS Inc., Chicago, IL). Fisher's exact test was used to differentiate between the lethal and survival cases of malignant MSF for: age, gender, time from disease onset to hospital admission, pre-morbid conditions, signs and symptoms, etc. Independent simple t-test was used to compare the mean values of the laboratory parameters between the lethal and survival cases of malignant MSF. $P<0.05$ (two tailed) was considered statistically significant.

IV. Results and Discussion

A number of studies have reported severe/malignant MSF and complications [5, 6, 10, 11, 12, 13, 15, 16]. In order to simplify and standardize the definition of MSF forms in severity, we developed a classification of MSF clinical forms and proposed a scheme to determine the severity of the disease. The proposed scheme was based on a set of criteria, defining severity [8]. In our research, malignant forms of MSF were defined as "Forms with multi-organ involvement (malignant)".

Regarding the laboratory parameters, most of the patients with malignant forms of MSF had anemia - 43(78.18%), leukocytosis - 37(67.27%) with a shift to the left - 34(61.81%), thrombocytopenia - 48(87.27%), and hypofibrinogenemia - 28(50.90%); prothrombin time (PT) was prolonged only in 9(16.36%) out of all patients, whereas thrombin time (TT) and activated partial thromboplastin time (APTT) were extended in 31(56.36%) of them. In a large proportion of patients hyperbilirubinemia was noted 35(63.63%), and nearly all had elevated ALT and/or AST serum levels 51(92.72%). In more than half of the patients - 31(56.36%) the total protein levels were below normal values. The same referred to patients with elevated levels of blood urea nitrogen and creatinine 33(60.00%). Nearly all patients had decreased albumin 52(94.54%), sodium 49(89.09%) and calcium 49(88.09%) serum levels.

It was interesting to compare the mean levels of the laboratory parameters between the deceased and survivors from malignant MSF in order to assess their relative weight in the disease outcome (**Table 1).** Deceased patients had significantly higher leukocyte count with a shift to the left and higher serum levels of blood urea nitrogen and creatinine. Compared to survivors, they had significantly lower values of fibrinogen and larger prolongation of TT. In the mean values of the remaining laboratory parameters, no significant differences were found between the deceased and surviving patients. Yet, thrombocytopenia was more pronounced in fatal cases, irrespective of the fact that the difference was not statistically significant.

Table 1 Laboratory parameters of patients with malignant forms of Mediterranean spotted fever

Laboratory parameters	**MSF malignant forms death n=19**	**MSF malignant forms survivor n=36**	**Statistic**	
	Mean±SEM	**Mean±SEM**	**P**	**S/NS***
Hb g/l	102.77±11.14	114.11±7.35	>0.05	NS
Er x10^{12}/l	3.22±0.27	3.64±0.23	>0.05	NS
Leuk x10^{9}/l	19.03±3.05	11.33±1.31	<0.05	S
Bands %	21.33±3.06	11.44±2.21	<0.05	S
Segs %	62.22±2.04	60.77±2.76	>0.05	NS
PLTx10^{9}/l	60.22±10.72	86.88±14.56	>0.05	NS
Fibrinogen g/l	1.67±0.28	2.75±0.30	<0.05	S
PT %	74.33±2.00	77.53±4.44	>0.05	NS
□ □sec	24.88±1.50	20.40±1.13	<0.05	S
A□ □ □sec	36.90±3.25	35.66±1.92	>0.05	NS
Bilirubin □mol/l	47.04±12.30	64.61±15.74	>0.05	NS
ALT U/l	188.33±56.75	213.88±39.78	>0.05	NS
AST U/l	270.88±74.96	199.77±37.97	>0.05	NS
Total protein g/l	60.55±5.09	59.38±4.21	>0.05	NS
Albumin g/l	27.66±1.69	28.54±4.07	>0.05	NS
Ure □ mmol/l	38.00±5.85	20.34±5.41	<0.05	S
Creatinine mmol/l	520.33±108.3	226.77±73.35	<0.05	S
Na mmol/l	128.00±2.94	132.77±1.16	>0.05	NS
Ca mmol/l	1.77±0.09	1.65±0.18	>0.05	NS

Legend: Hb – Hemoglobin; Er - Erythrocytes; Leuk – Leukocytes; Segs - Segmented Neutrophils; PLT - platelets; PT- prothrombin time; TT- thrombine time; APTT - Activated partial thromboplastin time; ALT – alanine aminotransferase; AST - aspartate aminotransferase; Bilirubin micromoles per litre (μmol/l);
*** S/NS =** significant/not significant

Some epidemiological features and main clinical signs and symptoms of our MSF' patients are presented in Table 2. All patients had a sudden onset with fever, chills, myalgia, headache, and other flu-like symptoms. In all patients, three to four days after the onset of symptoms, a specific maculopapular rash developed, typically starting on the trunk and spreading out to the extremities. It involved the hands and feet in 49 patients (89.09%). Forty one (74.5%) patients presented with tache noire, and conjunctiva was the likely port of entry in 4 cases. Cracks on fingers, incurred in the process of tick removal from pet dogs were the site of penetration in 10 cases.

The study was focused on the presence and prevalence rates of certain clinical and/or epidemiological characteristics in patients with fatal outcomes, compared to survivors from malignant MSF. It was found out that: age over 45 years, delayed hospital admission (longer than 6 days after the onset of symptoms), presence of pre-morbid underlying conditions as alcohol abuse, diabetes mellitus and hypertension, as well as failure to start or to complete appropriate antibiotic treatment were risk factors for fatalities. Regarding the main clinical signs and symptoms, none was prevalent in patients with malignant MSF from group I compared to patients from group II. Involved organ systems and main characteristic symptoms and signs (comparatively between the two groups) are shown in Table 2.

able 2 Clinical and epidemiological features and main clinical symptoms in patients with malignant forms of Mediterranean spotted fever. Comparative assessment of parameters in fatalities (group I) and survivors (group II) in malignant forms of Mediterranean spotted fever.

Parameters	**MSF total ases N=55**		**MSF lethal ases N=19 Group I**		**MSF survivors N=36 Group II**		**Fisher's exact test**		
	N	**%**	**N**	**%**	**N**	**%**	**P**	**Odds ratio**	**95% CI**
Age >45 years	33	60.0	17	89.47	16	44.44	=0.001	10.625	2.13-52.95
More than 6 days to hospital admission	29	52.7	17	89.47	12	33.33	<0.0001	17.00	3.36 -86.00
Pre-morbid underlying conditions*	17	30.9	15	78.94	2	5.55	<0.0001	63.75	10.5 -386.93
Failure to start or complete appropriate treatment	15	27.27	11	57.89	4	11.11	=0.0004	11.00	2.76 -43.82
Temperature over 39^0	53	96.4	19	100.00	34	94.44	=0.53	2.826	0.13 - 61.95
Tache noire	41	74.5	17	89.47	24	66.66	=0.103	4.250	0.84 - 21.50
Hemorrhagic rash	47	85.45	16	84.21	30	83.33	=0.70	1.70	0.31 - 9.38
Myalgia/arthralgia	50	90.90	19	100.00	31	86.11	=0.15	6.810	0.35 –130.15
Headache	52	94.54	19	100.00	33	91.66	=0.543	4.075	0.199 –83.16
Vomiting	44	80.00	18	94.73	26	72.22	=0.18	3.269	0.63 – 16.80
Abdominal pain	30	54.54	9	47.36	21	58.33	=0.57	0.6429	0.21 – 1.96
CNS involvement:	55	100.00							
Mental confusion – "Typhus state"	49	89.09	19	100.00	30	83.33	= 0.08	8.311	0.44 –156.09
Delirium/seizures/ stupor/coma	24	43.63	12	63.15	12	33.33	= 0.04	3.429	1.07 – 10.95
Pulmonary involvement:	32	58.18							
Interstitial pneumonia	29	52.72	13	68.42	16	44.44	= 0.15	2.708	0.84 – 8.72
ARDS*	3	5.45	3	15.78	0	0.00	= 0.03	15.485	0.75 –317.44
Hard violation of the acid-base balance	17	30.90	13	68.42	4	11.11	<0.0001	17.333	4.19 - 71.73
Myocardial involvement:	17	30.90							
ECG abnormalities	16	29.09	8	42.10	8	22.22	= 0.21	2.545	0.76 – 8.48
Myocarditis**	17	30.90	13	68.42	4	11.11	< 0.0001	17.333	4.19 –71.72
Hepatic involvement:	51	92.72							
ALT/AST increased levels	51	92.72	16	84.21	35	97.22	= 0.11	0.152	0.014 – 1.58
Jaundice	35	63.63	11	57.89	24	66.66	= 0.58	0.687	0.22 – 2.16
Digestive tract involvement:	13	23.63							
Gastrointestinal bleeding	8	14.54	6	31.57	2	5.55	= 0.01	7.845	1.40 – 43.97
Pancreatic involvement	5	9.09	4	21.05	1	2.77	= 0.04	9.333	0.96 – 90.68
Renal involvement:	33	60.00							
Very high urea and creatinine levels	33	60.00	17	89.47	16	44.44	=0.001	10.025	2.13 – 52.95
Acute renal failure	30	54.54	16	84.21	14	38.88	=0.001	8.381	2.05 – 34.11

Legend:

CI -Confidence interval; **MSF** – Mediterranean spotted fever; *ARDS – acute respiratory distress syndrome;

** Myocarditis - according to clinical setting and/or histological data;

CNS involvement is the acknowledged hallmark of malignant forms of MSF [10, 11, 12, 13]. Altered mental status of variable degree was present in all of our patients, ranging from cognitive slowing and somnolence to apathy or confusion – termed by classical authors as «Status typhosus ". The latter was equally present in the fatality group similarly to MSF survivor group. Typhoid mental condition is likely to progress to more severe CNS deterioration as delirium, stupor and coma, indicative of meningoencephalitis and/or brain edema. These symptoms were significantly more frequent in the deceased patients, compared to survivors and consequently appeared as risk factors for patients with malignant MSF.

Pulmonary involvement, presenting as interstitial pneumonia, was often seen in MSF patients [14] It was present in 29(52.72%) of our malignant forms of MSF, without statistical difference between the two studied groups. Acute respiratory distress syndrome (ARDS) however was present only in the group of lethality and appeared as one of the most important risk factors for death [15, 16].

Myocarditis is an uncommon, however severe occurrence in MSF, and only few cases have been reported in the literature [17, 18]. Myocardial involvement was found in about one third of the patients with malignant form of MSF. Myocarditis, diagnosed clinically and instrumentally, as well as based on histology proved to be a risk factor for mortality as it appeared several times more frequently in deceased than in survivors from malignant MSF.

Several studies have stated a high frequency of liver functional impairment in the course of MSF [19]. Based on increased ALT and AST activity, complicity of the liver occurred in almost all patients, and jaundice - in more than half of them. However, both findings showed no prevalence in deceased patients compared to survivors from malignant MSF.

Hemorrhages in the gastrointestinal tract are serious, although considered uncommon complication of vasculitic changes in malignant forms of MSF [20, 21, 22]. Gastrointestinal bleeding was a real risk factor for fatal outcome in our patients. Severe pancreatic damage (histological data in 4 deceased patients) and clinically suspected in only one of the survivors, was also a serious risk factor for death in malignant MSF.

Involvement of the kidneys was found in approximately 60% of the patients with malignant MSF. It presented with a significant increase in the serum urea and creatinine levels. Acute renal failure (ARF) was demonstrated at approximately the same rate. Both conditions were nearly twice as common in deceased compared to surviving patients and presented real risk factors for the lethal outcome in the most severe forms of MSF, the so-called malignant forms [23, 24].

V. CONCLUSION

Long time overlooked as a serious disease, at present, it is known that MSF had a false benign reputation. In this report we managed to identify the prognostic factors for mortality or survival in malignant forms of MSF. This approach is justified as the diagnosis in such cases is frequently a problem, resulting in delayed treatment. Early diagnosis and appropriate antibiotic treatment may reduce the risk of complications.

Conflict of Interests: There is no conflict of interests regarding the publication of this paper

REFERENCES

[1]. R o v e r y C, Brouqui P, Raoult D. Questions on Mediterranean spotted fever a century after its discovery. Emerg. Infect. Dis., 14 (9), 2008, 1360-7.

[2]. Parola P, Paddock CD, Socolovschi C, Labruna MB, Mediannikov O, Kernif T, Abdad MY, Stenos J, Bitam I, Fournier PE, Raoult D. Update on tick-borne rickettsioses around the world: a geographic approach. Clin. Microbiol. Rev., 26(4), 2013, 657-702.

[3]. Baltadzhiev IG, Popivanova NI. Some epidemiological features of the Mediterranean spotted fever re-emerging in Bulgaria. Folia Med (Plovdiv). 54(1), 2012, 36-43.

[4]. Levin ML, Killmaster LF, Zemtsova GE. Domestic Dogs (Canis familiaris) as Reservoir Hosts for Rickettsia conorii. Vector Borne Zoonotic Dis. 12 (1), 2012, 28-33.

[5]. Raoult D, Gallais H, Ottomani A, Resch JP, Tichadou D, De Micco P, Casanova P. [Malignant form of Mediterranean boutonneuse fever. 6 cases]. Presse Med. 12(38), 1983, 2375-8.

[6]. Mouffok N, Parola P, Lepidi H, Raoult D. Mediterranean spotted fever in Algeria–new trends. Int J Infect Dis, 13, 2009, 227–35.

[7]. Serbesov V, Alexandrov E. Active influencing of the epidemiological process of Marseille fever in Bulgaria. J Hig Epidemiol Microbiol Immunol, 17, 1973, 445-52.

[8]. Baltadzhiev IG, Popivanova NI, Stoilova YM, Kevorkian AK. Mediterranean spotted fever - classification by disease course and criteria for determining the disease severity. Folia Med (Plovdiv), 54(4), 2012, 53-61.

[9]. Brouqui P, Bacellar F, Baranton G, Birtles RJ, Bjoërsdorff A, Blanco JR, Caruso G, Cinco M, Fournier PE, Francavilla E, Jensenius M, Kazar J, Laferl H, Lakos A, Lotric Furlan S, Maurin M, Oteo JA, Parola P, Perez-Eid C, Peter O, Postic D, Raoult D, Tellez A, Tselentis Y, Wilske B; ESCMID Study Group on Coxiella, Anaplasma, Rickettsia and Bartonella; European Network for Surveillance of Tick-Borne Diseases. Guidelines for the diagnosis of tick-borne bacterial diseases in Europe. Clin Microbiol and Infect., 10(12), 2004, 1108–32.

[10]. Aliaga L, Sánchez-Blázquez P, Rodríguez-Granger J, Sampedro A, Orozco M, Pastor J. Mediterranean spotted fever with encephalitis. J Med Microbiol., 58(Pt 4), 2009, 521-5.

[11]. Baltadzhiev I, Boev I, Dineva A, Gocheva A, Kazakova T, Tsoneva A. [Meningitis and meningoencephalitis caused by Rickettsia conorii]. Medical Review, 49, 2, 2013, 73-7.

[12]. Demeester R, Claus M, Hildebrand M, Vlieghe E, Bottieau E. Diversity of Life-Threatening Complications due to Mediterranean Spotted Fever in Returning Travelers. Journal of Travel Medicine, 17(2), 2010, 100-4.
[13]. Alioua Z, Bourazza A, Lamsyah H, Erragragui Y, Boudi O, Karouach K, Ghfir M, Mossedaq R, Sedrati O. Neurological feature of Mediterranean spotted fever: a study of four cases. Rev Med Intern, 24(12), 2003, 824-9.
[14]. Walker DH, Crawford CG, Cain BG. Rickettsial infection of the pulmonary microcirculation: the basis for interstitial pneumonitis in Rocky Mountain spotted fever. Hum Pathol., 11, 1980, 263-72.
[15]. Escolar F, Sampériz AL, Rubio MT, Alonso JL. Non-cardiogenic pulmonary edema associated with boutonneuse fever. Med Clin (Barc.), 98(13), 1992, 517.
[16]. Arméstar F, Mesalles E, Manciño JM, Matas L. [Acute respiratory distress syndrome secondary to malignant Mediterranean boutonneuse fever]. Med Intensiva. ,33(6), 2009, 306.
[17]. Ben Mansour N, Barakett N, Hajlaoui N, Haggui A, Filali T, Dahmen R, Fehri W, Haouala H. [Acute myocarditis complicating Mediterranean spotted fever. A case report]. Ann Cardiol Angeiol (Paris), 63 (1), 2014, 55-7.
[18]. Colomba C, Saporito L, Colletti P, Mazzola G, Rubino R, Pampinella D, Titone L. Atrial fibrillation in Mediterranean spotted fever. J Med Microbiol., 57 (Pt 11), 2008, 1424-6.
[19]. Walker DH, Staiti A, Mansueto S, Tringali G. Frequent occurrence of hepatic lesions in boutonneuse fever. Acta Trop., 43(2),1986, 175-81.
[20]. Ruiz-Beltrán R, Herrero-Herrero JI, Walker DH, Cuñado-Rodríguez A. Mechanism of upper gastrointestinal hemorrhage in Mediterranean spotted fever. Trop Geogr Med., 42(1), 1990, 78-82.
[21]. Pereira MJF, Romãozinho JM, Sofia C. Mediterranean spotted fever with involvement of the gastrointestinal tract. BMJ Case Rep. 2013; doi:10.1136/bcr-2013-200186.
[22]. Rombola F. Mediterranean spotted fever presenting as an acute pancreatitis. Acta Gastroenterol Belg., 74(1), 2011, 91-2.
[23]. Shaked Y, Shpilberg O, Samra Y. Involvement of the kidneys in Mediterranean spotted fever and murine typhus. Q J Med., 87(2), 1994, 103-7.
[24]. Montasser DI, Zajjari Y, Alayoud A, Bahadi A, Aatif T, Hassani K, Hamzi A, Allam M, Benyahia M, Oualim Z. [Acute renal failure as a complication of Mediterranean spotted fever]. Nephrol Ther., 7(4), 2011, 245-7.