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Presentation and outcome of tuberculous meningitis in adults in the province of Castellon, Spain: a retrospective study

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SUMMARY

The aim of this study was to describe the epidemiological and clinical features of tuberculous meningitis in the province of Castellon, Spain. Retrospective analysis was done of all cases attended during the last 15 years. The following groups of variables were assessed: sociodemographic data, medical antecedents, clinical presentation, imaging study results, analyses, cerebrospinal fluid microbiology, treatment, and outcome. Twenty-nine cases were included. Median of age of patients was 34 years, and 17 (59%) were males. HIV infection was present in 15 cases (52%), fever, the most common symptom, occurred in 27 (93%), nuchal rigidity was noted in only 16 (55%), and syndrome of inappropriate ADH secretion (SIADH) occurred in 13 cases (45%). Chest radiograph was abnormal in 15 cases (52%). Anaemia was found in 22 subjects (76%), hypoalbuminaemia in 18 (62%) and hyponatraemia in 15 (52%). Macroscopic aspect of cerebrospinal fluid was normal in 17 cases (65%). Acid-fast stain was positive in only one case (4%). Two patients presented resistance to anti-tuberculous medications. Twelve patients (41%) died and eight (28%) presented sequelae. An association was found between death as outcome and presence of SIADH and lower level of serum cholesterol. Tuberculous meningitis is a rare and frequently difficult to recognize disease, which results in significant morbidity and mortality. We found an association of mortality with SIADH and lower level of serum cholesterol.

INTRODUCTION

Tuberculosis (TB) has re-emerged in the last two decades in developed countries, mainly due to the HIV epidemic and immigration [1, 2]. Central nervous system involvement by the disease is estimated to occur in 5–10% of patients, with tuberculous meningitis (TM) as the most common manifestation [3–5].

TM usually results from the haematogenous spread of primary or post-primary pulmonary infection, or from the rupture of a subependymal tubercle into the subarachnoid space. The disease may present acutely with altered sensorium and neck rigidity, or much more subtly with malaise, headache and minimal mental change. For that reason, in many patients, the disease is difficult to recognize, and a high index of suspicion is necessary to establish the diagnosis. Unfortunately, when TM goes unrecognized and without early treatment, mortality and permanent disability rates are high [5, 6].

Descriptive studies of TM are useful for understanding the impact of the disease and to determine possible changes in its presentation over time, which may be useful for optimization of medical care for the condition. In recent years, a few reports of TM in the adult population have been reported worldwide.

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In general the condition remains a serious complication of TB, although prognosis is nowadays better than it was in earlier reports, probably due to improved medical care [7, 8].

Research in this field in Spain is scant. In a review of the literature of the last 10 years, we found only two reports of TM cases, both of which concerned children [9, 10]. Therefore, we undertook this study to describe the epidemiological and clinical features of TM in adults, and to assess the changing pattern of the disease over time in our institution. We also attempted to determine factors associated with TM-related mortality.

METHOD

Study design

This study consisted of a retrospective analysis of all cases of TM diagnosed from 1 January 1991 to 31 December 2005 in the five hospitals of Castellon, a province of 500 000 inhabitants, situated in the North of the Comunidad Valenciana, Spain. The ethnic background of almost all the population of Castellon is Caucasian.

Recovery of cases

Cases of TM were recovered with the help of the electronic databases of the Medical Records Department (MRD) of each of the five institutions. The databases include all admissions, classified in accordance with the Spanish version of The International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) [11]. All cases with ICD-9-CM code 013 which relates to patients aged >14 years were initially searched, and those corresponding to TM were selected. The cerebrospinal fluid (CSF) results database of the Department of Microbiology, Hospital General of Castellon, where all microbiology specimens are processed in the province of Castellon, and the admissions databases of the departments of Medicine, Neurology, Neurosurgery, and Infectious Disease of all five hospitals were also searched, and cases of TM were also selected, if they had not been found in the MRD database. The medical records of all selected cases were reviewed, and all confirmed or probable cases of TM in adults were included in the study. A case was considered confirmed if *Mycobacterium tuberculosis* was isolated in the CSF or if nucleic acid of *M. tuberculosis* was detected in the CSF. A case was considered as probable if: (*a*) the clinical picture was suggestive of TM, (*b*) CSF laboratory results or meningeal biopsy were compatible with TM, (*c*) diagnostic tests excluded other aetiologies, and (*d*) a clinical response to anti-tuberculous treatment was observed.

In compliance with Spanish regulations regarding confidentiality, no personal data that could allow identification of patients was used throughout the study.

Study variables

From each case of TM the following variables were recovered and assessed: (*a*) sociodemographic data: year of occurrence, hospital attended, and patient's age, gender and nationality; (*b*) patient's medical antecedents: previous episodes of TB, human immunodeficiency virus (HIV) infection, intravenous drug use (IVDU), alcohol abuse, diabetes mellitus, use of immunosuppressant medications, and presence of other immunodeficiencies; (*c*) clinical presentation of TM: main symptom, duration of symptoms before diagnosis, duration of hospitalizations before diagnosis, presence/absence of nuchal rigidity, level of consciousness (alert, lethargic or comatose), highest axilar temperature, early complications of TM [seizures, syndrome of inappropriate ADH secretion (SIADH), cranial nerve palsy or other], presence/absence of active TB in other locations, presence/absence of other infections and duration of hospitalization; (*d*) imaging studies: computed tomography (CT) scan findings, magnetic resonance imaging (MRI) findings, and chest radiograph results; (*e*) analyses results: blood biochemistry, blood cell counts and coagulation tests, as well as CD4 cell count and HIV RNA in HIV-infected patients, urine analyses results, CSF macroscopic aspect, CSF analyses results (glucose, protein, white blood cell count and differential); (*f*) CSF microbiology results: acid-fast stain, culture and/or nucleic acid test; (*g*) treatment: anti-tuberculous medications, other medications, other treatments, duration of anti-tuberculous treatment, and resistance to anti-tuberculous medications; and (*h*) outcome (complete recovery, sequelae or death). For the purpose of this study, the diagnosis of SIADH was established when hyponatraemia was present and the disorder was not explained by any other cause.

Statistical analyses

A Little's missing completely at random (MCAR) test was used to assess deviation from randomness in

Table 1. *Blood analysis results of the patients with tuberculous meningitis*

	Median	IQR	Number of cases (%) with values outside normal range
Glucose (mg/dl)	109	97–124	7 (24)
BUN (mg/dl)	13	10–17	2 (7)
Creatinine (mg/dl)	0·8	0·7–1·0	1 (3)
Sodium (mmol/l)	133	127–138	15 (52)
Potassium (mmol/l)	4·2	3·7–4·5	9 (31)
Chloride (mmol/l)	98	93–101	14 (48)
Calcium (mg/dl)*	8·7	7·9–9·0	12 (41)†
Total bilirubin (mg/dl)	0·6	0·4–1·0	5 (17)
Total proteins (g/dl)	6·7	6·2–7·9	16 (55)
Albumin (g/dl)	3·2	2·7–3·9	18 (62)
Total cholesterol (mg/dl)	164	124–194	8 (28)
Triglycerides (mg/dl)	107	78–133	6 (21)
LDH (IU/l)	342	295–467	10 (34)
Alkaline phosphatase (IU/l)	142	104–194	3 (10)
ALT (IU/l)	28	19–50	11 (38)
WBC count ($\times 10^9$/l)	4·9	3·8–7·1	16 (55)
Haemoglobin (g/dl)	10·7	9·5–12·0	22 (76)
MCV (fl)	84	80–89	5 (17)
Platelet count ($\times 10^9$/l)	246	152–292	6 (21)
Lymphocyte count ($\times 10^9$/l)	750	345–1090	7 (24)
INR	1·0	1·0–1·2	5 (17)
aPTT (s)	28	26–33	1 (3)
Fibrinogen (mg/dl)	298	229–360	8 (28)
HIV RNA (copies/ml, $\log_{10}$)‡	3·8	3·2–5·8	n.a.
CD4 cell count (per mm^3)‡	112	44–129	n.a.

IQR, Interquartile range; BUN, blood urea nitrogen; LDH, lactate dehydrogenase; ALT, alanine aminotransferase; WBC, white blood cell; MCV, mean corpuscular volume; INR, international normalized ratio, i.e. prothrombin time ratio adjusted by international reference thromboplastin; aPTT, activated partial thromboplastin time; n.a., not applicable.

* Uncorrected for serum albumin.

† One patient had hypercalcaemia while the other 11 had hypocalcaemia.

‡ Data available from HIV-infected patients only.

missing values of study variables. Missing values were imputed using the expectation-maximization (EM) method.

Continuous variables were summarized as median and interquartile range (IQR). For univariate analyses the following tests were employed as required: χ^2 or Fisher's exact test for discrete variables, and the Mann–Whitney *U* test for continuous variables. Variation among different years over the study period was assessed with the following tests: χ^2 for discrete variables and Kruskal–Wallis for continuous variables.

A multivariate, forward-stepwise (Wald) logistic regression analysis was performed on deceased or living as outcome. The following variables were included as predictors (independent variables): gender, age, year of TM occurrence (before or after 2000), hospital where TM was attended (Hospital General of Castellon, or other), HIV status, any previous diagnosis of TB, duration of symptoms before diagnosis of TM was established, duration of hospitalization before diagnosis, presence/absence of nuchal rigidity, any diminished level of consciousness, highest axillar temperature, presence/absence of neurological complications, presence/absence of SIADH, duration of hospitalization, any abnormal findings in CT scan or MRI of the head, chest radiograph normal/abnormal, results of blood analysis (Table 1), macroscopic aspect of CSF (clear or not), CSF analysis results (glucose, protein, white blood cells and percentage of white blood cells), simultaneous presence/absence of TB in organs other than the central nervous system, anti-tuberculous treatment with three or four drugs, any treatment with corticosteroids, and any neurosurgical procedures performed.

All reported P values were two-sided, at the 0·05 significance level.

RESULTS

A total of 26 possible TM cases were recovered from the electronic databases of the MRDs, and eight more cases were found with the other searched databases. Four cases were excluded because they did not meet the established diagnostic criteria of confirmed or probable TM, and one further case was excluded because it concerned a child. Therefore, a total of 29 cases were finally included in the study; 22 were confirmed cases and seven were probable cases. Every case pertained to a different patient.

Nine missing values on continuous variables (1%) were found not to be deviated from randomness ($P=1$), and were replaced by imputed values. There were no missing values among discrete variables.

Sociodemographic data

Annual incidence of TM varied from 0 to 5 cases. In the first 5 years there were seven cases, in the second 5 years eight cases, and in the third 5 years 14 cases. Differences in incidence of the disease in years over the study period was not significant ($P=0·579$). The overall median of age of patients was 34 years (IQR 28–57, range 17–78); difference in age in years was not significant ($P=0·291$). Seventeen of the study patients (59%) were male and 12 (41%) were female. Twenty-eight patients (97%) were Spaniards and one (3%) was Romanian.

Patients' medical antecedents

Five patients (17%) had presented TB previously, all of them at least 1 year before the diagnosis of TM; in three patients the infection was located in the pleura and in the other two in the lungs. All five patients had received adequate anti-tuberculous medication. HIV infection was present in 15 patients (52%), IVDU in 12 (41%), diabetes mellitus in four (14%), alcohol abuse in three (10%) and other immunodeficiencies in three (10%). All 15 patients with HIV infection (100%) had been diagnosed with the condition previously, but only five (33%) were taking anti-retroviral medication. Incidence of TM among HIV-infected patients was similar before and after the availability of highly active anti-retroviral therapy. When TM was diagnosed, two patients were taking immunosuppressant medications: one of them chemotherapy for acute lymphoblastic leukaemia, and another one corticosteroids for systemic lupus erythematosus. Seven patients (24%) had no relevant medical antecedents.

Clinical presentation of TM

TM presented with fever in 27 patients (93%), headache in 20 (69%), diminished level of consciousness in 20 (69%), vomiting in 11 (38%) and general constitutional symptoms in 10 (34%). Before the diagnosis of TM was established symptoms were present for a median of 21 days (IQR 11–45), and patients were hospitalized for a median of 6 days (IQR 2–15). On physical examination nuchal rigidity was present in only 16 patients (55%); level of consciousness was normal in eight patients (28%), lethargic in 16 (55%) and comatose in five (17%); confusion or delirium was observed in eight (28%). Median of highest axillar temperature was 38·9 °C (IQR 38·5–39·4); axillar temperature remained below 38 °C all of the time in six patients, and below 37 °C in two patients (7%).

Early complications of TM included SIADH which presented in 13 patients (45%), cranial nerve palsies in five (17%), seizures in two (7%), myelitis in one (3%), cerebellar syndrome in one (3%), aphasia in one (3%), right hemiparesis in one (3%), right-hand paresis in one (3%), bilateral amaurosis in one (3%), and cognitive impairment in one (3%). Incidence of SIADH was similar in HIV-infected patients (six cases, 40%) than in non-HIV-infected patients (seven cases, 50%) ($P=0·59$). At the time when diagnosis of TM was established, a total of seven patients (24%) presented simultaneously clinical manifestations of TB in other organs: all seven in the lungs and one also in the kidneys. *M. tuberculosis* grew in the sputum of all seven patients, and in the urine of the patient with kidney infection. No co-infections with other microorganisms were diagnosed in patients with TM, although bacteria which were considered to be contaminants grew in specimens of six patients (21%). Median duration of hospitalization was 32 days (IQR 15–44).

No relevant differences were found between HIV-infected and HIV-uninfected patients regarding clinical presentation. Anti-retroviral therapy was continued in four of the five patients who were already being treated before the diagnosis of TM was made. Such therapy was initiated in four more patients at about the same time that anti-tuberculous

treatment was instituted. All eight patients who received anti-retroviral therapy were treated with two nucleoside analogue reverse transcriptase inhibitors, seven patients received efavirenz and one patient received saquinavir boosted with ritonavir. No case of immune reconstitution syndrome or toxicity due to medications was described in the medical records of the HIV-infected patients.

Imaging studies

A CT scan of the head was performed in 21 patients (72%); the study was normal in seven (33% of the patients who underwent the procedure), showed hydrocephalus in eight (38%), brain ischaemic lesions in four (19%) and revealed other abnormalities in five (24%). A MRI of the head was performed in 13 patients (45%); the study was normal in three (23% of the patients who underwent the procedure), showed hydrocephalus in six (46%), meningeal enhancement in six (46%), small enhancing lesions in four (31%), and brain ischaemic lesions in two (15%). A MRI of the spine was performed in five patients (17%); the study was normal in one (20% of the patients who underwent the procedure), showed meningeal enhancement in four (80%), syringomyelia in one (20%), and an intradural extramedullary tuberculoma in one (20%). Chest radiographs were performed in all patients; the study was normal in 14 cases (48%), showed lung infiltrates in 11 (38%), pleural effusion in four (14%) and other abnormal findings in two (7%).

Analyses results

Table 1 shows blood analysis results, including biochemistry, cell counts and coagulation tests, as well as CD4 cell count and HIV RNA in HIV-infected patients. Urine analyses showed abnormal sediment and/or proteinuria in 10 patients (34%).

CSF was unavailable from three patients, who were diagnosed as TM by meningeal biopsy. CSF was available from all the other 26 patients (90%). Macroscopic aspect was normal in 17 out of 26 (65%), turbid in seven (27%) and haemorrhagic in two (8%). CSF analysis results (median and IQR), were as follows: glucose (24, 17–32 mg/dl), protein (125, 98–246 mg/dl) and white blood cell count (148, 65–388 per mm^3); mononuclear cells predominated in 16 patients (61%).

No relevant differences were found between HIV-infected and HIV-uninfected patients in analysis results.

CSF microbiology results

Of the 26 patients with available CSF specimen, acid-fast stain was positive in only one (4%), culture grew *M. tuberculosis* in 21 (81%) and nucleic acid test, which was performed in seven patients, was positive in one (4% of the total of subjects).

Treatment and outcome

Anti-tuberculous treatment consisted of four drugs in 22 patients (76%) and three drugs in six (21%); one patient (4%) died before TM was suspected and therefore received no anti-tuberculous medication. Resistance test to anti-tuberculous medications were performed in 19 patients (65%); one patient presented resistance to rifampin and pyrazinamide and one patient to rifampin only, while all other patients presented no resistance. Both patients with resistance had a past history of treatment for TB. The patient with rifampin and pyrazinamide resistance died.

Other medications included dexamethasone in 16 patients (55%) and anticonvulsants in four (14%). Three patients (10%) underwent ventricle-peritoneal shunt because of hydrocephalus.

Twelve patients (41%) died during hospitalization, eight (28%) presented sequelae 6 months later, and nine (31%) completely recovered. The sequelae were: paresis in five patients (62% of those who presented sequelae), cognitive impairment in four (50%), and amaurosis in one (12%). Of the 17 patients who survived, nine (53%) took anti-tuberculous treatment for 9 months and the other eight (47%) took it for 1 year.

Multivariate analysis

A five-step multivariate, forward-stepwise (Wald) logistic regression analysis provided the following results: A test of the full model against a constant-only model was statistically reliable ($P<0{\cdot}001$), indicating that independent variables reliably predict the dependent variable. The variance in dependent variable accounted by independent variables was good, with Cox & Snell $R^2=0{\cdot}554$. Prediction success was also good with 83% of deceased cases and 82% of living cases correctly predicted, for an overall success rate of

Table 2. *Logistic regression analysis of outcome deceased or alive as a function of independent variables*

	Predictors	*B*	Wald	*P*	OR	95% CI
Step 1	Serum cholesterol*	−0·032	5·807	0·016	0·969	0·944–0·994
Step 2	SIADH*	−3·684	6·324	0·012	0·025	0·001–0·444
	Serum cholesterol	−0·046	6·758	0·009	0·955	0·922–0·989
Step 3	SIADH	−9·502	4·050	0·044	0·000	0·000–0·781
	Serum cholesterol	−0·103	3·648	0·056	0·902	0·812–1·003
	GGT*	0·023	3·563	0·059	1·023	0·999–1·048
Step 4	SIADH	−236·163	0·000	0·990	0·000	0·000
	Serum glucose*	1·800	0·000	0·991	6·048	0·000–3·935
	Serum cholesterol	−1·730	0·000	0·990	0·177	0·000–3·671
	GGT	0·711	0·000	0·993	2·036	0·000–9·415
Step 5	SIADH	−4·452	5·480	0·019	0·012	0·000–0·485
	Serum glucose	0·041	2·897	0·089	1·042	0·994–1·091
	Serum cholesterol	−0·053	5·583	0·018	0·949	0·908–0·991

B, Regression coefficient; *P*, significance of Wald; OR, odds ratio; CI, confidence interval; SIADH, syndrome of inappropriate ADH secretion; GGT, gamma glutamyl transpeptidase.
* Predictor entered at each step.

83%. Table 2 shows regression coefficients, Wald tests, odds ratios, and confidence intervals of odds ratios for each independent variable at each step. An association was found between deceased outcome and presence of SIADH and lower level of serum cholesterol. No association was found with the other assessed variables.

A validation multivariate, backward-stepwise logistic regression analysis gave the same results and associations.

DISCUSSION

TM, a rare disease in developed countries [12], presented in adults in the province of Castellon at an incidence of about 2 cases per year, i.e. 0·4 cases/100 000 adult inhabitants, according to our data. Although there were more cases of TM during the last 5 years than in the previous two 5-year periods, differences in years were not significant, probably due to the relatively short period of observation and the overall small number of cases. Despite the fact that paediatric patients were not included, the condition predominantly affected young people.

In developed countries, TB in general [1, 2], and TM in particular [12], are especially prevalent among the immigrant population. In contrast, in our study, only one patient (3%) was a native of a country other than Spain. The ethnic background of all patients was Caucasian.

In most of our patients, TM was the first presentation of TB, although 17% of patients had suffered pulmonary or pleural disease previously. Approximately 50% of our patients were HIV-infected, a percentage higher than the reported in most other studies [12–14]. This probably reflects the relatively high prevalence of HIV infection in Spain compared with other countries. In accord with another report from Spain [15] most of our HIV-infected patients were IVDU, a condition which is clearly associated with an increased risk of TB [1, 2]. We found no differences in clinical presentation, laboratory features or outcome between HIV-infected and HIV-uninfected patients, probably due to the relatively small sample size.

In our study, TM presented with diminished level of consciousness in the majority of patients, while nuchal rigidity was absent in most cases. Symptoms were generally present several weeks before diagnosis was established. These results highlight the protean, and frequently difficult to recognize presentations that TM may adopt [16]. SIADH, the most commonly observed complication, occurred in almost 50% of our patients. Simultaneous clinical manifestations of TB, in organs other than the central nervous system, occurred in 25% of cases. Median duration of hospitalization was about 1 month. We found no change in the mode of presentation of TM in our patients over time.

As in other reports [17, 18], imaging studies of the head revealed abnormalities in a majority of patients, and chest radiographs showed pathological findings in 50% of cases. Blood analysis abnormalities were common, especially hyponatraemia, hypoalbuminaemia

and anaemia, which were present in >50% of patients. Urine analysis abnormalities were present in 33% of our patients, probably reflecting the non-specific alterations of acute disease commonly seen in urine. TB of the urinary tract could also explain some of those alterations, but *M. tuberculosis* was isolated from urine in only one patient.

Macroscopic aspect of CSF was normal in the majority of our patients, in agreement with other reports of TM [19]. CSF analysis revealed results similar to those of other studies, with moderately decreased glucose, mild to moderately increased protein and mild to moderately increased white blood cell count; mononuclear cells predominated in the CSF of >50% of our patients. Acid-fast stain and nucleic acid tests were positive in a minority of patients. In most subjects, the diagnosis of TM was suspected on the basis of the clinical picture and results of CSF analysis, and confirmed afterwards by CSF culture. These results illustrate the difficulties that exist in establishing early diagnosis of the disease, a key circumstance to improving the treatment and prognosis of TM [20–23].

Anti-tuberculous therapy consisted of four drugs in most of our patients. Resistance to anti-tuberculous medications compared to other studies [23] was uncommon. Only 50% of patients received corticosteroids, and 10% received ventricle-peritoneal shunts because of hydrocephalus [24]. Outcome was especially poor in our study, with a mortality of 41% and persistence of sequelae in 28% of patients. Most other published reports give a better prognosis for TM [12, 21, 25, 26]. Inadequate use of corticosteroids among our patients might be a potential explanation [6].

A multivariate analysis of our data suggested an association of increased mortality with the presence of SIADH and lower cholesterol serum levels. Other studies have also found an association of mortality with those same factors in patients with TB [27, 28]. Low cholesterol, as well as hypoalbuminaemia, presumably reflect malnutrition, a condition commonly associated with TB, which could favour the increased mortality among our patients [29]. HIV infection, a condition that has been related to a worse prognosis of TM in other studies [13], was not associated with increased mortality in the present study. In two recent studies, one with paediatric patients from India and the other with adult patients from Spain, mortality of TM was also similar in HIV-infected or HIV-uninfected subjects [30, 31].

Due to the characteristics of the present study, with a relatively small number of cases, and a retrospective design, we may have failed to identify other important prognostic factors [14]. In brief, our study shows that TM is a rare and frequently difficult to recognize disease, which results in significant morbidity and mortality.

DECLARATION OF INTEREST

None.

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