

Factors affecting the prognosis of Albanian adult patients with generalized tetanus

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SUMMARY: Factors affecting the prognosis of Albanian adult patients with generalized tetanus.

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Background. *Despite systematic vaccination of the population, tetanus continues to be a health problem in Albania, as in some other developing countries. In this study, our intent was to evaluate prognostic factors relating to death in adult patients with generalized tetanus.*

Methodology and patients. *All the patients (60) included in the study were hospitalized at the regional hospitals of Shkodra and Korça, and the University Hospital Centre "Mother Theresa" of Tirana, Albania, during the period of 1984-2004. They had a mean age of 49.1±14.4 years, 43 (71.7%) were males and 40 (66.6%) of them lived in rural areas. The mean incubation period was 12 days and the case-fatality rate (CFR) was 38.3%.*

Results. *The CFR in patients with an onset period ≥2 days was 21.7% and in those with <2 days was 48.6%, OR=0.29 (p<0.05). Patients >50 years old had a CFR=60.87% (OR=7, p<0.05). We found the high CFR to be significantly associated with urban residency, male gender, complicated wound, head localization, fever ≥ 38.4 °C, tachycardia > 120 beats/min, and hypertension.*

Discussion. *The main prognostic factor of those analyzed in our study appeared to be the onset period and the age of the patients. We didn't find significant differences in CFR in patients with different incubation periods. Clinicians must take into account that wound complication and localization, tachycardia and hypertension, high fever, male gender and urban residency significantly influence the prognoses of adults with generalized tetanus.*

RIASSUNTO: Fattori prognostici in una popolazione di pazienti adulti albanesi affetti da tetano generalizzato.

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Introduzione. *Nonostante la vaccinazione sistemica della popolazione, il tetano continua ad essere un problema sanitario in Albania e in altri paesi in via di sviluppo. Scopo del nostro studio è la valutazione dei fattori di letalità in pazienti adulti affetti da tetano generalizzato.*

Metodologia e pazienti. *Tutti i 60 pazienti inclusi nello studio sono stati ricoverati, nel periodo 1984-2004, negli Ospedali Regionali di Shkodra e Korça e nel Centro Ospedaliero Universitario "Madre Tersa di Calcutta" di Tirana in Albania. La loro età media era di 49,1±14,4 anni; 43 erano uomini (71,7%) e 40 (66,6%) vivevano in aree rurali. Il periodo medio di incubazione del tetano è stato di 12 giorni e il tasso di letalità (case-fatality rate, CFR) del 38,3%.*

Risultati. *Il CFR in pazienti con periodo tra l'inizio della malattia e la comparsa del primo spasmo parossistico (onset period) ≥ 2 giorni è stato del 21,7% e del 48,6% in quelli con tale periodo < 2 giorni (OR 0,29, p < 0,05). In pazienti di età > 50 anni il CFR è stato del 60,87% (OR 7, p < 0,05 vs età inferiore). Un tasso di letalità elevato è significativamente associato a residenza in area urbana, genere maschile, ferita complicata e/o del capo, febbre ≥ 38,4 °C, tachicardia > 120 battiti/minuto e ipertensione.*

Discussione. *Tra quelli analizzati, i più importanti fattori prognostici di letalità sono risultati l'età e l'onset period. Non abbiamo invece rilevato differenze statisticamente significative del CFR in pazienti con differente periodo di incubazione. Va comunque considerato che sede e stato della ferita, tachicardia e ipertensione, febbre elevata, il genere maschile e la residenza in aree urbane hanno un impatto significativo sulla prognosi di soggetti adulti affetti da tetano generalizzato.*

KEY WORDS: Tetanus - Prognostic factors - Case-fatality rate.
Tetano - Fattori prognostici - Tasso di letalità.

Introduction

Due to immunization programs, tetanus incidents have decreased significantly, but the disease continues to be a health problem in developing countries. In developed countries, most of the cases with tetanus and deaths occur in elderly (1–7), but in the developing countries most of the deaths from tetanus occur in younger population

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and neonates (5, 8). During the period of 1961–2001, tetanus incidents in Albania varied at 4.8–0.06 cases per 100 000 people per year (9). Neonatal deaths caused by tetanus in Albania have been reduced significantly as a result of tetanus immunization programs for pregnant women (9). However, tetanus remains a potential risk for adults' health in Albania due to the high occurrence rate of traffic and work related accidents, wide spread agricultural activity, lack of periodic systemic booster immunization schedules every 10 years, migration of population without health documents, and incomplete coverage of the country's territory with health services.

Generalized tetanus is the most common form of the disease and is characterized by painful contractions of masticators (trismus) and neck muscles. Despite advances in medical care, the death rate in generalized tetanus continues to be higher than 20% (10–12). Different authors have revealed that CFR can be influenced by patient's age, incubation and onset time, type and localization of injury, clinical signs, and delays in treatment and prophylaxis (13–17). In this study, we intend to evaluate prognostic factors related to deaths in adult patients with generalized tetanus in Albania.

Methodology and patients

Data source

In this retrospective analysis of the data obtained from the three largest hospitals of Albania; University Hospital Centre "Mother Theresa" of Tirana, Regional Hospital of Shkodra, and Regional Hospital of Korça, we analyzed the medical records of all the reported cases of patients with generalized tetanus that were hospitalized during the period of 1984–2002.

Study definitions

The conclusive diagnosis for each patient was made clinically by carefully excluding other possibilities. In order to ensure that all the diagnoses were reliable, we took into consideration each patient's clinical presentation, immunization history, history of wound or injury, chronic wounds (e.g., decubitus ulcer, diabetic ulcers), any recent drug use, tattooing, body piercing, occupation and hobbies.

Patients

Of the 60 patients, 43 (71.7%) were males, 40 (66.6%) patients lived in rural areas, and only one was a drug user. They had an overall mean age of 49.1 ± 14.4 years (range: 14–81 years), and 37 (61.7%) were 10–49 years old. Most (53.8%) of the cases had deep and suppurated injury, 29 (48.3%) patients had lower extremities injury, 21 (35%) upper extremities injury, 4 (6.6%) head injury, 3 (5%) body injury, and 1 (1.6%) patient developed tetanus after septic abortion. One (1.6%) patient developed tetanus after abdominal surgery, and another developed tetanus with an unknown injury.

All patients received passive immunization with 10 000–100 000 U heterolog tetanus antiserum, and only 15 (25%) received active immunization with tetanus toxoid. 32 (53.3%) patients received surgical treatment of the wound. All the patients were treated with 1–5 mg/kg benzodiazepine (diazepam) and as needed Phenobarbital, Chlorpromazine and/or opiates. In 18 (30.0%) patients, mechanical ventilation was used since generalized spasms were not control-

led with drugs. All the patients were treated with antibiotics; 46 (76.7%) with penicillin, 7 (11.7%) with metronidazole, 4 (6.7%) with cephalosporin, and the others with ampicilline and aminoglycosidics.

The most common complications were those of the respiratory system in 23 (38%) of the patients (infections and pulmonary embolism), and cardiovascular system in 21 (35%) of the patients (cardiac arrest, cardiac arrhythmias and arterial hypertension).

Statistical analysis

The statistical analyses were performed by using Microsoft Excel and S.P.S.S. version 10.0. We applied a descriptive and analytical statistical evaluation of the data extracted from the medical records. All the variables suspected to have correlations with complications, therapy, or prognoses of the tetanus are presented in arithmetical means and standard deviations or percentages and proportions depending on the type of the data.

We also calculated the correlation coefficients between the different parametric variables. The means were compared with the Student's t-test and the proportions with the Chi-Square test. We used Binary Logistic Regression models to evaluate the relationships between independent and dependent variables. Assumptions of the Binary Logistic Regression models were confirmed with Likelihood Ratio and Hosmer-Lemeshow tests. Possible collinearities were evaluated with linear regression models. We considered significant all the differences with a $p < 0.05$.

Results

The overall CFR was 38.33%. It was significantly higher among patients ≥ 50 years old with an OR=7.00 ($p < 0.05$) and a Spearman's rank correlation coefficient of 0.1 ($p < 0.05$), which indicates a weak correlation but nonetheless statistically significant (Table 1).

The mean incubation period was 12 ± 7.9 days (range, 2–28 days) and 41 (68.33%) patients had an incubation period of ≤ 10 days. CFR appeared to be lower in patients with a longer period of incubation (OR=0.30) but this was not statistically significant ($p > 0.05$) (Table 1).

Twenty-three patients (38.2%) with an onset-period ≥ 2 days had a significantly lower CFR (OR=0.29, $p < 0.05$) compared with the others, and this was accompanied with a strong correlation coefficient ($R = 0.71$, $p < 0.05$). Patients that resided in urban areas and females had a higher risk of death with ORs of 2.36 and 1.90, respectively ($p < 0.05$) (Table 1).

Patients with suppurated wounds resulted to be at a greater (2.41 times higher) risk of death compared with the others ($p < 0.05$). In this case, the Spearman's rank correlation coefficient was 0.24 ($p < 0.05$). There were no significant differences when we compared CFR of patients with upper and lower limb wound localization, but patients with other localizations (uterus, trunk, head) were significantly more prone to dying (OR=1.90, $p < 0.05$) (Table 1).

With regard to clinical signs, patients that had High Arterial Blood Pressure during the disease appear-

TABLE 1

Parameter	Total (n)	Fatality				Comments
		n	Rate (%)	OR	p value	
Age (years)						
10-29	11	2	18.18	1.00	-	CFR is significantly higher in age-group ≥ 50 years old. Spearman's rank correlation coefficient, $R=0.1$, $p<0.05$.
30-49	26	7	26.92	1.66	> 0.05	
≥ 50	23	14	60.87	7.00	<0.05	
Incubation (days)						
0-10	41	19	46.34	1.00	-	CFR is lower for incubation periods ≥ 11 days but this is not statistically significant.
≥ 11	19	4	21.05	0.30	> 0.05	
Onset-period (days)						
< 2	37	18	48.6	1.00	-	CFR is significantly lower for longer onset-periods. Spearman's rank correlation coefficient, $R=0.71$, $p<0.05$.
≥ 2	23	5	21.7	0.29	<0.05	
Wound complication						
Non-suppurated	23	6	26.09	1.00	-	CFR is significantly higher in patients with infected wounds. Spearman's rank correlation coefficient, $R=0.24$, $p<0.05$.
Suppurated	37	17	45.96	2.41	<0.05	
Wound localization						
Foot	29	10	34.48	1.00	-	CFR is significantly higher in localizations closer to the head.
Hands	21	8	38.09	1.17	> 0.05	
Others	10	5	50.00	1.90	<0.05	
Residence						
Rural	40	13	32.5	1.00	-	The CFR is significantly higher in the patients coming from the urban areas.
Urban	20	10	50.0	2.36	<0.05	
Sex (n)						
Male	43	15	34.9	1.00	-	The female tetanus patients are significantly at a greater risk for death.
Female	17	8	47	1.9	<0.05	
Temperature ($^{\circ}\text{C}$)						
<38.4	25	8	32.00	1.00	-	CFR is significantly higher in patients with a body temperature ≥ 38.5 . Spearman's rank correlation coefficient, $R=0.23$, $p<0.05$.
≥ 38.5	35	15	42.86	1.30	<0.05	
Blood leukocyte count (mm^3)						
$<10,000$	28	8	28.57	1.00	-	Patients with a Blood Leukocyte Count ≥ 10000 haven't a significantly higher CFR compared with the others.
$\geq 10,000$	32	15	46.87	2.46	> 0.05	
Blood pressure (mmHg)						
$<150/100\text{mmHg}$	50	15	30	1.00	-	The CFR is significantly higher in patients with a Arterial Blood Pressure $>150/100\text{mmHg}$. Spearman's rank correlation coefficient, $R=0.18$, $p=0.006$.
$\geq 150/100\text{mmHg}$	10	8	80	19.4	<0.001	
Heart rate (b/min)						
<100	44	13	29.5	1.00	-	The CFR is significantly higher in patients that have a Heart Rate ≥ 100 min. Spearman's rank correlation coefficient, $R=0.48$ $p=0.003$.
≥ 100	16	10	62.5	4.02	<0.05	
Total	60	23	38.6			

red to be at a significantly greater risk of death compared to the other patients ($\text{OR}=19.4$, $p<0.001$), but in this case we found a weak correlation ($R=0.18$, $p=0.006$). Cases with tachycardia ≥ 100 beats per minute were significantly associated with higher risk of death ($\text{OR}=4.02$,

$p<0.05$) and had a correlation coefficient of $R=0.48$ ($p=0.003$) (Table 1). Patients with a body temperature $\geq 38.5^{\circ}\text{C}$ had a higher CFR than the others with $\text{OR}=1.30$ ($p<0.05$) and a Spearman's rank correlation coefficient of $R=0.23$ ($p<0.05$).

Patients who received surgical treatment of the wound had a CFR of 1.4 times higher than those who did not. There were no outcome differences in CFR between patients who were treated with penicillin and those treated with metronidazole, but all four patients treated with cephalosporin survived.

Discussion

The World Health Organization (WHO) in 1990 reported that every year approximately 1 000 000 people suffer from tetanus resulting in more than 715,000 deaths per year (18). In Albania, the number of tetanus instances during the period of 1961-2001 varied at 4.8-0.06 cases per 100,000 per year (9). A similar occurrence ratio (1.6 per 1,000,000 per year) was found in Italy by Stroffolini et al, in 1991 (19).

As stated by other authors, the occurrence rate of tetanus depends on climate, environment, and the country's economic development (17, 20). Therefore, the reason that tetanus can occur in all seasons in Albania can be attributed, among other causes, to the country's Mediterranean climate and its rural population. Since almost all cases of tetanus in Albania occur in adults, we can infer that inadequate or even lack of immunization could be the primary causes for this observation, but unfortunately this cannot be serologically supported due to lack of studies in this field.

In our study, we had 2.5 times more males than females. This ratio can be attributed to the higher frequency rate of males' engagement in hard labor, especially in agriculture and construction, and to the country's regular immunization program for pregnant women. Such data shows the same tendency as revealed by some other authors (21-23). In our study we have only one patient (1.6%) with post-abortion and none with post-partum tetanus, revealing the low occurrence rate of maternal tetanus in Albania. This coincides with the low occurrence rate of neonatal tetanus which may be due to the regular immunization of pregnant women (24).

The overall CFR in our study was 38.33%, similar to some studies done in France and Poland in 1991 and 1994, respectively (25, 26), but much higher compared to the CFR in Denmark in 1970s (1) and Finland (3) which varies 9-11 percent. These variations in CFR may be due to several reasons. One of the reasons may be the differences in the definitions between generalized and non-neonatal tetanus, as the last one includes localized tetanus which has a very low CFR.

49 patients (81.7%) were ≥ 30 years old and probably contracted the disease due to lack of booster shots every 10 years. However, 11 patients (18.3%) aged 10-29 years old probably contracted the disease at least partly from not having been administered the last shot of

the primary immunization program, as this age group normally has the highest level of tetanus antibody (27, 28). This appears to be in contrast with observations in developed countries where the majority of tetanus cases occur in persons over 50 years of age (1-7).

Patients ≥ 50 years old had a significantly higher CFR when compared with those in the 10-29 years old age group (OR=7.00 and $p < 0.05$) with a Spearman's rank correlation coefficient of $R = 0.1$, ($p < 0.05$). Several causes may explain the higher CFR in this age group. Cardiovascular complications is one reason since they tend to occur more frequently in patients ≥ 50 years old ($p < 0.05$). In addition, within this age group, the CFR was significantly higher in patients with high arterial blood pressure or tachycardia ($p < 0.05$). Interestingly, the CFR of patients ≥ 50 years old was similar to those reported from studies in India and Nigeria. However, our CFR was significantly lower for the other age groups (29-30).

The CFR was lower in patients that had an incubation period ≥ 11 days but this wasn't statistically significant ($p > 0.05$). Similar results (with different incubation periods) were found in other studies (23, 31). CFR was also significantly lower for longer onset-periods ≥ 2 days ($p < 0.05$), yielding a strong Spearman's rank correlation coefficient of $R = 0.71$ ($p < 0.05$).

Patients that had suppurated wounds were at a greater (2.41 times higher) risk of death than the others ($p < 0.05$). The CFR was higher in patients that had wounds localized closer to the head, with OR=1.90 ($p < 0.05$). Other authors have revealed the same tendency (17).

Interestingly, the CFR was higher in patients that resided in urban areas with an OR=2.36 ($p < 0.05$). It's difficult to hypothesize what factors may have influenced this difference, especially since after 1991 a considerable part of rural population, which was represented by some of the patients in our study, moved to urban areas.

In this study we found out that females with generalized tetanus were at a higher risk of death compared to males (OR=1.9, $p < 0.05$). This may demonstrate that the variation in the death rate between genders may be due to the differences in exposure and immunizations and not in the sensitiveness to the tetanus toxins as some authors hypothesized (32,33). Compared to the others, the CFR of patients with high fever ($\geq 38.5^\circ\text{C}$) had an OR=1.3, ($p < 0.05$) with a Spearman's rank correlation coefficient equal to 0.23 ($p < 0.05$). However, the CFR of those with higher leukocyte blood count (≥ 10000 cells/ml) had a non-significant OR=2.46 compared to the others.

In conclusion, we think that in order to further decrease the occurrence rate of tetanus in Albania, further studies must be conducted with the purpose of correcting the inadequacies of the immunization program and

improving its application process. Important factors that influence the generalized adult tetanus prognosis in our study are; age, onset period, wound complication and localization, residency, gender, heart rate, blood pressure

and high fever. These factors must be taken into account by the different health services departments, in order to lower the country's high CFR due to generalized adult tetanus.

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