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Abstract - Tetanus is a life-threatening nervous disorder, which is now a rare condition in the developed world, thanks to effective immunization programmes and proper treatment of wounds and traumatic injuries. The generalized form, which consists of muscle spasms and autonomic dysfunction is the most common and most severe clinical form. We describe the case of a patient in whom generalized tetanus was diagnosed and successfully treated. The autonomic features are described and are accompanied by tako-tsubo cardiomyopathy, a form of heart failure which is caused by adrenergic stimuli.

Keywords - Tetanus, Clostridium tetani, Tako-tsubo cardiomyopathy, Apical ballooning

Introduction
Tetanus is a nervous system disorder characterized by muscle spasms and is caused by a toxin-producing anaerobic bacteria (Clostridium tetani, C tetani) [1]. Tetanus can present in four clinical patterns: generalized, local, cephalic and neonatal [1]. Tetanus is a life-threatening nervous disorder, especially in its most common generalized form. Besides muscle spasms, the generalized form consists of autonomic features due to catecholamine release. In the developed world, the condition is now rare but in spite of adequate vaccination programmes and improved care of traumatic injuries, it does still exists, mainly in the elderly female population.

Case report
An 80-year old woman was referred to our emergency department because of progressive stiffness in her neck and difficulty with swallowing and opening her mouth. Three weeks prior to admission, she had been gardening and afterwards noticed some small wounds on her lower limbs which she took care of herself. Her medical history consisted of surgery to both breasts for a benign cause and obstructive pulmonary disease for which she used theophylline and inhalation therapy with fluticasonepropionate-salmeterol. The patient did not use any other drugs, was a non-smoker and did not drink any alcohol.

On clinical examination we saw an older woman with a good general condition. Her vital parameters were not compromised (non-invasive blood pressure 155/87mmHg, respiratory rate 18/min and saturation on pulse oximetry of 97%). Mobility of the limbs appeared normal, but we noticed a severe hyperextension of the neck with no possibility of flexion. The patient could only open her mouth by 1.5 centimetres. The examination of lungs, heart, abdomen, skin and vessels showed no abnormalities.

The results of the biochemistry tests did not show any sign of inflammation (CRP 2.0 mg/L, erythrocyte sedimentation rate 20mm/h). The renal and liver function tests were normal and in subsequent blood samples, we saw a mild elevation in cardiac markers (Creatinine kinase 413 U/L, CK-MB mass 19.5 µg/L, Troponin I 2.37 µg/L). Serial electrocardiography examination showed a sinus tachycardia and a mild elevation of the ST-segment in the anterior leads (figure 1).

Localised tetanus was suspected and the patient was treated with human tetanus immunoglobulins (TIG) (Tetabuline®, 3000IE), tetanus-vaccination (Tedivax®, 3 injections over two weeks) and was nursed in a private room to diminish external sensory triggers. To control the muscle spasms, the patient was treated with benzodiazepines (diazepam). Due to the development of autonomic dysfunction in the first 24 hours after admission, the patient was also treated with labetolol and magnesium sulphate. Autonomic crises consisted of tachycardia, severe but instable arterial hypertension and secondary pulmonary oedema with severe combined metabolic (lactate) and respiratory acidosis, with the latter due to cardiac asthma. These autonomic crises were accompanied by muscular spasms in the jaw and neck regions. On day 3, we decided to intubate in controlled circumstances. Urgent airway management was expected to be difficult in an episode of autonomic crisis combined with cervical rigidity. The crises were treated with morphine sulphate (5 mg subcutaneously) or fentanyl (50 µg intravenously), both with good result.

On echocardiography, we surprisingly saw apical ballooning (Tako-tsubo cardiomyopathy, TTC) which would explain the frequent episodes of pulmonary oedema (figure 2). On day 6 of admission a percutaneous tracheostomy was performed. Despite sedation with diazepam combined with propofol, tetanic crises developed frequently until three weeks after admission; neuro-muscular blocking agents were administered whenever necessary. We started early full parenteral nutrition and early enteral nutrition. Enteral nutrition was increased to conform to our local guidelines and parenteral nutrition was gradually reduced and stopped when the enteral calorie intake was sufficient.

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Für den Fall der Tetanus: Eine klinische Beobachtung

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Zusammenfassung - Tetanus ist eine lebensbedrohliche neurologische Erkrankung, die in den entwickelten Ländern eine seltene Konsequenz ist, dank effektiver Impfung und dem ordnungsgemäßen Betrieb von Wunden und traumatischen Verletzungen. Der allgemeine Form, der durch Muskelzuckungen und autonome Funktionen gekennzeichnet ist, ist die am häufigsten und schwersten klinische Form. Wir beschreiben den Fall einer Patientin, bei der der diagnostizierte Fall von generalisiertem Tetanus erfolgreich behandelt wurde. Die autonomen Merkmale werden beschrieben und sind von Tako-Tsubo-Kardiomyopathie begleitet, einer Form des Herzens, die durch adrenerge Stimuli ausgelöst wird.

Schlüsselwörter - Tetanus, Clostridium tetani, Tako-Tsubo-Kardiomyopathie, Apikale Ballonung

Einführung
Tetanus ist eine neurologische Erkrankung, die durch Muskelspasmen und autonome Funktionen gekennzeichnet ist. Die allgemeine Form ist die am häufigsten und schwersten klinische Form. Wir beschreiben den Fall einer Patientin, bei der der diagnostizierte Fall von generalisiertem Tetanus erfolgreich behandelt wurde. Die autonomen Merkmale werden beschrieben und sind von Tako-Tsubo-Kardiomyopathie begleitet, einer Form des Herzens, die durch adrenerge Stimuli ausgelöst wird.

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Hospitalisation in the ICU unit was complicated by haemoptysis which was caused by aspiration lesions in the upper bronchial tree. After one month on the ICU, the patient was weaned off the ventilator and sedation. She did not develop any further tetanic crises and the abnormal autonomic features disappeared. The cardiac function normalised both clinically and on echocardiography.

After 34 days hospitalization, the patient was transferred to a high dependency unit and three days later, she was transferred to the ward. She was admitted to a rehabilitation programme on our geriatric ward where her functional state further improved. She was discharged 82 days after her initial admission to the emergency department. She left the hospital in good general condition and went home where she still lives independently.

Discussion

Tetanus is a nervous system disorder characterized by muscle spasms and is caused by a toxin-producing anaerobic bacteria (Clostridium tetani, C. tetani) [1]. Tetanus can present in four clinical patterns: generalized, local, cephalic and neonatal [1]. Although the symptoms of muscle spasms in this case were localized (trismus and hyperextension of the neck region), our patient suffered from the most common and severe generalized form of tetanus which includes symptoms of autonomic hyperactivity. In this patient, the adrenergic storm led to TTC and secondary pulmonary oedema. TTC, or apical akinesis, is a condition that mimics acute anterior ST elevation myocardial infarction with transient ST elevation in the chest leads and transient akinesis of the apex and distal half of the anterior, inferior, and lateral heart walls with compensatory hyperkinesis of the basal walls. The syndrome was first described in 1990 and the name of the disorder is taken from the Japanese name for an octopus trap (Takostubo) with the morphological features of the patient’s heart resembling this pot with a round bottom and narrow neck [2]. This condition is frequently precipitated by severe psychological or physical stress [3-5]. The condition predominantly occurs in postmenopausal women [5]. The pathogenesis of the disorder is not well understood. Several mechanisms for this syndrome have been postulated: firstly a direct myocardial injury induced by the release of catecholamines which led to a neurogenic or adrenergic stunned myocardium. This mechanism is identical to that seen in acute cerebrovascular accidents, due to myocardial enervation of sympathetic nerve ends which results in high intracardial catecholamine levels. Likewise, the mechanism is comparable to situations of emotional or physical stress and pheochromocytoma in which systemic catecholamines release can cause TTC [6,7]. Excessive levels of catecholamines induce microvascular spasm, myocardial damage and hypocontractility which leads to ventricle wall motion abnormalities [8,9]. The apical myocardium has a greater density of sympathetic nerves and therefore it is more responsive to adrenergic stimulation and more vulnerable to sudden catecholamine storms. This may explain why the apical wall is most affected and the base is spared. Plasma catecholamine concentrations in TTC patients are 2-3 times higher compared to patients admitted for myocardial infarction [10]. Secondly, coronary microvascular dysfunction might lead to apical akinesia syndrome. Coronary microvascular function has been shown to be diffusely abnormal [11,12] in the absence of significant obstructive coronary lesions. Thirdly, the evidence that the syndrome is almost exclusive to the female gender which points to the hormonal environment as one of the explanatory arguments for the syndrome. For example, the influence of the reduced oestrogen levels on the sympathetic neurohormonal axis, coronary reactivity and endothelial function may play a role.

Diagnostic criteria for TTC (or Transient Left Ventricular Apical Ballooning Syndrome) were proposed by the Mayo Clinic and

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**Figure 1.** ECG: transient mild ST-elevation in anterior leads V2-V4 during tetanic crisis

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**Figure 2.** Transthoracic echocardiography image: characteristic apical ballooning with apical akinesis and reduced left ventricular function (ejection fraction 30%).
include: electrocardiographic abnormalities (either ST-segment elevation or T-wave inversion), transient akinesis or dyskinesis of the left ventricular apical and mid-ventricular segments, with wall-motion abnormalities extending beyond a single epicardial vascular territory and the absence of obstructive coronary artery disease. Exclusion criteria for the syndrome are a recent head trauma, intracranial bleeding, pheochromocytoma, myocarditis and hypertrophic cardiomyopathy [3,13]. Angiography is obligatory, to exclude the presence of a culprit lesion and to show the characteristic akinesis of the apical part of the left ventricle [14]. We did not perform a coronary angiography in our patient, because the clinical picture of pulmonary oedema, the electrocardiographic changes and the elevated cardiac markers did not occur outside the tetanic crises and this makes a ST segment myocardial infarction less likely. But as a coronary obstructive lesion has not been ruled out, our patient does not fulfil the diagnostic criteria for TTC as described above. Therefore, we can only describe the clinical features as “apex affected cardiomyopathy”. However, the suggestion can be made that the cardiomyopathy might be due to high intracardial catecholamine levels due to an overactivity of the adrenergic nerve system which is affected by the tetanus toxin (TT). This mechanism can be compared to the neurogenic mechanism postulated as one of the possible explanations for TTC. Therefore, we suggest that TTC can be caused by tetanus. As far as we know, this has never been described before.

Due to the almost universal vaccination against tetanus of children in developed countries, the incidence of tetanus in our region of the world has dropped dramatically and steadily since 1940 [15]. Most patients who do contract the disease either lack a history of a full series of tetanus toxoid immunization or did not have their booster immunization. In our hospital, we have only diagnosed three cases of tetanus in the past ten years; all of these concerned older (more than 65 years of age) female patients – which is also seen in other European countries [15].

Tetanus occurs when spores of C tetani gain access to damaged human tissue. C tetani, an obligate anaerobic bacteria, is normally present in the gut of mammals and is widely found in soils. After inoculation, C tetani changes into a vegetative rod-shaped bacterium and produces the metalloprotease tetanosamin (or tetanus toxin (TT)). Through retrograde axonal transport, TT reaches the spinal cord and binds irreversibly to receptors and blocks neurotransmission by its cleaving action on membrane proteins involved in neuro exocytosis. The effect is disinhibition of neurons that modulate excitatory impulses from the motor cortex. Disinhibition of anterior horn cells and autonomic neurons leads to increased muscle tone, painful spasms and widespread autonomic instability. These effects are long-lasting, because recovery requires the growth of new axonal nerve terminals. After the death of the bacteria, TT is released and activated by bacterial or tissue proteases [16-18]. C tetani will not grow in healthy tissue as a combination of at least two factors should be present. These factors are e.g., a penetrating injury resulting in inoculation, co-infection with other bacteria, devitalized tissue, a foreign body or localized ischemia [1]. The incubation period may vary from one to three days to several months, with a median of 7-8 days. The incubation period depends on the distance from the location where the inoculation takes place to the central nervous system [19,20].

The treatment of tetanus includes five goals (halting the toxin production, neutralization of the unbound TT, control of muscle spasms, management of dysautonomia and general supportive measures) [1,21] and is best performed in an ICU where a critical care specialist is trained in the management of this disease. Unfortunately, little evidence exists to support any particular therapeutic intervention in tetanus. There are only nine randomized trials reported in the literature over the past four decades [15,16].

The TT production is halted by effective wound management and antimicrobial therapy (penicillin G, a cephalosporin or metronidazole [1, 22,24]). TIG should be administered as soon as possible to neutralize unbound TT (human TIG 3000-6000 IU intramuscularly or, as an alternative, pooled intravenous TIG [1,24] and all patients should receive active immunization through vaccination (3 doses of tetanus and diphtheria toxoid, spaced two weeks apart). Every ten years, subsequent tetanus doses should be given throughout adulthood [1,24]. Generalized muscle spasms are life-threatening, since they can cause respiratory failure, lead to aspiration and induce exhaustion. Several drugs may be used to control these spasms, for example, sedatives – benzodiazepines have been used traditionally but propofol may also control spasms and rigidity, and neuromuscular blocking agents such as pancuronium or boclofen. In addition, attention should be paid to where the patient is placed and to the control of light and noises, because external stimuli can induce spasms [1,24]. When higher doses of sedatives are necessary to control the spasms, ventilator assistance and airway protection are imperative [1,24]. Several drugs have been used to produce adrenergic blockade and suppress autonomic hyperactivity, for example, labetolol, esmolol and clonidine [1]. The use of magnesium sulphate infusions has been found to significantly reduce the requirement for other drugs to control muscle spasms as well as the need for calcium channel blockers for the treatment of cardiovascular instability [25,26]. Furthermore, morphine sulphate is commonly used to control autonomic dysfunction. The initial management of stress-induced cardiomyopathy is also largely supportive, including hydration and an attempt to alleviate the triggering physical or emotional stress. Although we didn’t perform a coronary angiography, we emphasize that in patients who present with a clinical picture consistent with an ST elevation myocardial infarction, the suspicion of stress-induced cardiomyopathy is not a reason to alter management. The significant majority of these cases are due to occlusion of a coronary artery and revascularization therapy should not be delayed. We recommend that such patients be managed in the conventional manner, either with urgent catheterization and percutaneous coronary intervention or with fibrinolytic therapy. The role of additional medications and the appropriate duration of therapy has not yet been established. Most experts favour at least the short-term use of standard medications for heart failure due to systolic dysfunction, with a therapeutic regimen consisting of beta blocking agents, in combina-
tation with angiotensin converting enzyme inhibitors or angiotensin 2 receptor blockers if the ejection fraction is less than 40% [3,14]. Catecholamines β adrenergic receptor agonists” (β AR agonists) are capable of recruiting the inotropic reserve and may restore cardiac performance of a stunned myocardium. In our case, how- ever, β AR agonists may be contra-indicated because of suspect- ed existing high serum levels of adrenaline during tetanus crisis and therefore, they should be avoided if possible, as these may make the condition worse. When the haemodynamic state is se- verely compromised, this is a challenging condition to treat [14]. As mentioned, we chose to treat our patient with labetolol instead of solely beta blocking agents. Labetolol, with dual alpha and beta blocking properties, might be favourable in the treatment of left ventricular failure due to apical ballooning syndrome sec- ondary to autonomic tetanic crises, not only to reduce afterload, but also to reduce the global sympathetic activity that induces the apical myocardial stunning. However, the treatment of these autonomic features with beta blocking agents remains controver- sial because of reports of sudden death [1]. A possible cause of mortality in cases of tetanic crisis treated with β blocking agents could be worsening of the cardiac performance (which is already compromised) leading to cardiogenic shock.

Because tetanus toxin is irreversibly bound to the tissues, supportive care is the main treatment for tetanus. Prolonged im- mobilization and mechanical ventilation in the ICU are common and these patients are predisposed to nosocomial infections, decubital ulcers, gastrointestinal bleeding and thromboembolic disease [1,24]. Due to the prolonged mechanical ventilation sometimes required, early tracheostomy after initial endotracheal intubation has to be considered [24]. Early nutritional support is mandatory because energy demands may be extremely high. As soon as the spasms are under control, physical therapy should be started as tetanus patients are left with disability from pro- longed drug-induced paralysis and immobilization [1].

Mortality-rates in non-neonatal tetanus in developing coun- tries range from 8 to 50 percent; in our hospital, however, two of the three patients died despite critical care management [27,28]. In contrast, prognosis of TTC is generally favourable. In-hospital mortality rates have ranged from 0 to 8 percent [3,5,29,30]. There was one in-hospital death and one late death in the largest pro- spective series of 88 patients in Japan [5]. Patients who survive the acute episode typically recover normal ventricular function within one to four weeks [5,10,29]. Mortality depends, among other things, on the severity of the disease.

Conclusion
Tetanus remains a life-threatening nervous disorder which is now rare in the developed world thanks to effective immunization pro- grammes and proper treatment of wounds and traumatic injuries. The treatment consists of halting the tetanus toxin production and neutralising the toxins and of providing supportive measures. The generalized form, which consists of muscle spasms and au- tonomic dysfunction is the most common and most severe clin- ical form. The tetanic crises consist of muscular spasms together with adrenergic stimulation. The latter can lead to haemodynamic instability, in this particular case due to TTC. Supportive mea- sures including intensive management of the autonomic features can save the lives of patients with this condition.

Abbreviations

β AR agonists β adrenergic receptor agonists
TTC tako-tsubo cardiomyopathy
TT tetanus toxin