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## Trismus, opisthotonus and risus sardonicus: Who remembers this disease?

*Trismo, opistótono e riso sardônico: quem se lembra dessa doença?*

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Tetanus, a disease so ancient that even Hippocrates spoke of it. Has it ceased to be or does it still exist? Does it still present itself as a problem to modern medical practice, or is it just a mere curiosity, a footnote in some book? Perhaps the question we should ask ourselves, as doctors, is if we have been neglecting tetanus... and if we have, equally, neglected the aspects related to its prevention and treatment. Beyond medical practice, are we not neglecting the generation and communication of knowledge about this pathology which is of such great relevance in the Brazilian context?

Let us begin from where medicine should always begin: the aspects pertaining to disease prevention and the promotion of health. Tetanus is an immuno-preventable disease, thus the mere occurrence of tetanus cases in the country demands reflection. Yes, there are cases of tetanus in Brazil and they are not few, as demonstrated by the data from the Brazilian Ministry of Health.<sup>(1)</sup> Let us remember that tetanus is a disease that must be duly reported so that its data is entered in the national epidemiologic alert system. Let's begin with the morbidity data and then proceed to lethality data. If we take the absolute annual numbers of tetanus cases supplied by the Ministry<sup>(2)</sup> and group them into ten year periods, we will observe the following distribution:

1) 10,993 cases of accidental tetanus in the decade comprised between 1990 and 1999 (with an annual average of 1099 cases per year, varying from 705 cases per year in 1998 to 1548 cases per year in 1990);

2) 4560 cases of accidental tetanus in the decade comprised between 2000 and 2009 (with an annual average of 456 cases per year, varying from 315 cases per year in 2009 to 608 cases per year in 2002).

Thus, over the years, one can see a decrease in the absolute number of accidental tetanus cases reported in the country. The more elaborate data from the state of Sao Paulo points towards the same trend. If we group the state's annual numbers<sup>(4)</sup> into decades we have:

1) 1,540 cases of accidental tetanus in the period comprised between 1980 and 1989 (an annual average of 154 cases), with incidence coefficients (per 100,000 inhabitants) varying between 0.44 (133 cases) in 1989 and 0.70 (171 cases) in 1984;

2) 4,560 cases of accidental tetanus in the period between 1990 and 1999, (an annual average of 96.9 cases), with incidence coefficients between 0.16 (57 cases) in 1998 and 0.43 (133 cases) in 1990;

3) 328 cases of accidental tetanus in the period comprised between 2000 and 2010, (an annual average of 32.8 cases), with incidence coefficients between 0.12 (47 and 46 cases in 2001 and 2002 and 0.05 (20 cases) in 2007.

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In the Sao Paulo state cases, besides the decrease in incidence one may also notice a clear predominance among males<sup>(5)</sup> and a high incidence in age groups above 50.<sup>(6)</sup> In these higher age groups, especially over 60, one can also observe a marked decrease among the incidence indexes over the years.<sup>(6)</sup> What could this phenomenon be attributed to? From 1999 onward, a series of government campaigns were implemented to call attention to adult vaccination, including efforts focused on vaccinating the more senior age groups. These actions included yearly vaccination against seasonal influenza which resulted in the opportunity to offer and update the strategy for vaccination against tetanus and diphtheria (the double adult vaccine or dT) within this target age group. The corresponding increase in vaccination coverage against tetanus had a direct impact on the disease's morbidity coefficients which, as displayed, presented a significant decrease.

Thus, the use of immunobiologics has revealed itself extremely relevant in preventing accidental tetanus, as expected. As a result, one cannot discuss tetanus without emphasizing the prevention issue. In this disease there is primary prevention, which is applied to the population to protect it from tetanus and there is secondary prevention which is applied to patients with a lesion, that is possibly a *C. tetani* infective focus, so they do not develop tetanus as a result of this lesion.

Let's begin with primary prophylaxis. The goal is to vaccinate the population and maintain its vaccines current. We must remember that a complete vaccine procedure with the tetanus toxoid consists of three primary doses, administered in childhood, followed by several booster shots applied throughout childhood and adolescence.<sup>(7)</sup> Following this basic scheme, an adult needs to be vaccinated preferably with the double adult (dT) vaccine every 10 years. Adults must, thus, always update their anti-tetanus vaccinations. As doctors, we must keep this preventive issue in mind so that we prescribe these vaccination updates to our patients. This medical practice applies not only to infectologists but to any doctor. Thus, when consulting a patient that presents hypertension, diabetes, depression or whatever pathology the doctor should perform an anamnesis with regards to the patient's vaccination, correcting it whenever applicable. Have we all, as doctors, done this in our clinical consultations?

Let's now resume searching for answers to the question with which we began this editorial, through which we will conclude that the question was not a rhetorical question but a substantive question that actually needs to be made: are we neglecting the prevention of tetanus? We have seen that at the level of collective health, governmental programs are not neglecting it, to the contrary, they are promoting

positive results that have reduced the incidence of tetanus throughout the Brazilian territory. What remains is that we consider issues pertinent to the health of individuals that visit our offices and clinics.

In this context – that of an individual patient's health – another issue that arises is secondary prophylaxis. All tetanus that presents itself to us in the ICU, having been seen by a doctor at the time of the focus, stands as a witness to preventative medical action that should have been taken, but wasn't. And this presents the opportunity for consideration of ethical and legal issues related to good professional practice. Whenever any type of lesion is encountered, proper anti-tetanus prophylaxis should always be administered and duly reported in the medical charts or emergency department records. Any lesion, no matter how simple it may seem, can be a tetanus focus. There are lesions that have a greater tetanogenic potential (such as lesions incurred by foreign bodies, infections, necrosis or collection resulting from animal bites, post manipulation abortions, burns, exposed fractures, among others) and lesions with lesser tetanogenic potential. Each of these will require greater or lesser rigor in prophylaxis, however, they will all require prophylaxis. There are several tables that summarize the proper prophylactic measures for the prevention of tetanus.<sup>(7)</sup> We can summarize them (always at the risk of oversimplifying) in the following situations if we have firm evidence that the patient has been properly immunized (which includes the primary three-dose-series and booster shots every 10 years), we understand that prophylaxis has been performed. It is only necessary to treat the lesion as best possible. If we understand that the patient has not been adequately immunized, we take the opportunity to vaccinate. However this is not sufficient in the case of lesions with greater tetanogenic potential, in which case, besides vaccination, passive immunization with, for example, anti-tetanus immunoglobulin should be applied. In any case, the adequate treatment of the lesion is important (debridement and suturing are recommended). It is worth mentioning that antibiotics do not perform anti-tetanus prophylaxis.

Thus, every one of the reported accidental tetanus cases could have been avoided if secondary prophylaxis had been properly administered when caring for the tetanus focus. Once again we should ask ourselves if we have not been neglecting tetanus prevention within our daily medical practice.

The issue of neonatal tetanus is also central to discussing prevention. As highlighted by Gomes et al.,<sup>(8)</sup> in this edition of RBTI, the issue of neonatal tetanus arises from two causes: insufficient immunization of the adult population and the difficulty that expectant mothers have to receive quality prenatal care. Every expectant mother should be (re)immunized during pregnancy to provide protective

antibodies to the fetus.<sup>(9)</sup> If every expectant mother is immunized, neonatal tetanus will be eradicated. But, after all, are there still neonatal tetanus cases in Brazil? The Ministry of Health's<sup>(10)</sup> data are clear. When grouped by decade, we have, in Brazil, 1,642 reported cases of neonatal tetanus in the period comprised between 1990 and 1999 (an average of 164.2 cases per year), 184 cases between 2000 and 2009 (18.4 cases per year) and seven cases in 2010, reported in the states of Acre, Para, Maranhao and Bahia. In 2009, the last cases were reported in Goias and Rio Grande do Sul; in 2008, in Rio de Janeiro; in 2007, in Parana; in 2006 and in Minas Gerais, Pernambuco, Piaui and Amazonas; in 2005, in Tocantins, Amapa, Ceara and Alagoas; in 2004, in Rio Grande do Norte; in 2003, Rondonia; in 2002, in Santa Catarina and Paraiba; in 2001, in Espirito Santo, Sergipe and Mato Grosso do Sul; in 2000, in the Federal District; in 1999, in Sao Paulo; in 1998 in Mato Grosso and, finally, in 1993, the last case in Roraima.<sup>(10)</sup>

These are important epidemiologic data that demonstrate the relevance of tetanus among us in terms of morbidity indexes. We should now consider the lethality indexes, in other words, depart from the field of prevention and enter the field of therapeutic considerations. For when preventive measures fail, we must deal with therapeutic measures.

Tetanus is a potentially serious disease that can lead to early death through restrictive and obstructive respiratory failure (one cannot breathe during spasms) or, further along, through issues that arise from tetanus itself (dysautonomias) or by means of a series of complications that belong to the intensive therapy context such as infection thromboembolism, several of which have been well discussed by Santos et al. in this issue of RBTI.<sup>(11)</sup> Tetanus lethality data are clearly evident in the history of cases registered in the State of Sao Paulo.<sup>(4)</sup> Between 1980 and 1989, 589 of the 1,540 reported cases died, a lethality rate of 38%; from 1990 to 1999, 351 patients died out of the 969 cases reported (a lethality rate of 36%); from 2000 to 2009, 117 patients died out of the 328 cases reported (a lethality rate of 35%). In 2010, the lethality rate was of 31% (5 deaths out of 16 cases).<sup>(4)</sup>

It should be noted that despite the decreasing indexes of tetanus, the rate of lethality remains frighteningly stable at around 35%. In age groups above 50, lethality can easily reach 100%.<sup>(12)</sup> If we factor in the neonatal tetanus cases in Sao Paulo state, rates of lethality are far higher:<sup>(13)</sup> from 1980 to 1989 there were 70 deaths among the 110 reported cases (a lethality rate of 64%), and from 1990 to 1999, seven deaths among the 12 reported cases (58%).

What have we intensive care physicians and infectologists done to treat tetanus and why haven't we been able to reduce its lethality over the years? We have certainly learned

to ventilate, to sedate, to relax, to use antimicrobials with expertise in the practice of intensive care, making use of all the technological and conceptual development that this area of medicine has witnessed over the last decades. However, we have not succeeded in reducing the lethality of tetanus in our intensive care.

This is something we should reflect upon. In this issue of RBTI we have a pioneering movement by the Brazilian Association of Intensive Medicine – AMIB that is publishing guidelines for the treatment of tetanus.<sup>(14)</sup> Organized by a panel of experts, these guidelines collect the best available evidences upon which to base medical practices and communicate them in the form of recommendations, thus proposing a sensible homogenization of conduct. These arise from hard, courageous work: the pertinent literature is vast and widely dispersed, distributed among hard-to-find publications, found in languages that are not the most common and involves local issues from countries that are still in development. This literature is abundant in the aspects of basic sciences that have to do with the effects of tetanospasmin within the presynaptic spaces which also serve as a methodological instrument for the study of this synaptic function and its mediators. This literature stands out with regards to the use of Immunobiologics (serums and vaccines), either as instruments of protective efforts or as methodological instruments in the research of the immune system and its response capabilities. Nevertheless, with regards to clinical and treatment aspects this same literature is dominated by anecdotal reports of cases and transversal case histories and rarely can one find double blind, randomized, multi-centric or other studies capable of generating any degree of firmer evidence. It should be noted, however, that the lack of precise evidence does not preclude from generating strong recommendations, as is seen in these proposed guidelines for the management of tetanus.<sup>(14)</sup> It is worth highlighting (and praising) the convenience (and propriety) of commissioning a panel of experts of diverse backgrounds and inflections, who are used to professionally dealing with the clinical patients of tetanus under different realities and traditions, with the task of drafting these guidelines. It was a comprehensive panel comprising southern, northeastern and other Brazilian regional accents as well as the tendencies and manias of both infectologists and intensive care physicians, which due to its testimonial nature could only produce guidelines that are appropriate to the Brazilian national reality. As a result these guidelines are, above all, precious.

Due to their nature of proposing and homogenizing, these guidelines also open up an intensive line of research that points in, at least, three directions. The first direction will be always to understand if the guidelines are worthy, in

other words, that we try to understand if their application will actually have an impact on the reduction of the unflinching historic lethality of tetanus in the Brazilian context. It is a pertinent question whose answer, we hope, will appear in future issues of RBTI. Litvoc et al.<sup>(15)</sup> studying the historical cases of accidental tetanus in the year of 1989 in Sao Paulo state, found lethality on the order of 49.5% when considering all hospitals, against 34.5% in a hospital with a specific reference unit for tetanus patients, in which one would suppose, there was a homogeneity of conduct. The difference did not reveal itself statistically significant, as the authors themselves recognize the limitations of the study for this type of conclusion. On the other hand, the study by Santos et al.,<sup>(11)</sup> published in this issue of RBTI, mentions an enviable lethality rate of 9.1%. As made clear above, this rate is well below the Brazilian national average. The authors demonstrate, without losing sight of the study's limitations, that at least 2/3 of the patients were classified as serious or very serious by tetanus gravity scores, in other words, it's probably not a case of low lethality due to the inclusion of case histories of less serious patients. The authors attribute the therapeutic success to "the multidisciplinary team's knowledge and specialization", besides the technological advances of intensive care therapy. Thus one may conclude that "specialization" is important and it remains to be seen if this specialization can be supplied or instrumentalized by guidelines elaborated by experts.

I would also highlight the importance of multidisciplinary in caring for tetanus patients as well as in the production and communication of knowledge, both in the publication by Santos et al.,<sup>(11)</sup> whose authorship included a physical therapist, as well as in the guidelines,<sup>(14)</sup> that specifically cover physical therapy treatment as one of their recommendations. This is the second direction for the research lines I mentioned:

interesting our colleagues from other health professions such as speech-language pathologists and nurses to produce knowledge on this subject. If, after all, the guidelines recommend an early tracheotomy of tetanus patients, how will the decannulation be performed? Is there a role for the speech-language pathologists in this regard? And if tetanus focuses can be dental, how should a dentist be involved in the multidisciplinary team?

The third and last direction of the lines of research inspired by the publication and implementation of these guidelines has to do with the production and collection of greater evidence in areas the guidelines have revealed as missing. Which score of gravity is more adequate or may serve as a predictor for tetanus? Which scheme or strategy of analgesia presents the best cost/benefit ratio for these patients? And, since there are pharmacoeconomic issues involved, what is the best anti-tetanus immunoglobulin dosage (500 or 5000 IU), after all? Should pacemakers be employed in cases of parasympathomimetic dysautonomias? Are benzodiazepines actually drugs of choice over curare as first-line treatment for muscular relaxation in tetanus? This is just a sampling of pertinent questions.

So now it seems that we are equipped to respond to the question with which we began this editorial: have we been neglecting tetanus? The answer is yes, if we, as doctors, have neglected to promote primary vaccination prophylaxis in our patients. Yes, if we, as doctors, have neglected promoting post-exposure prophylaxis in the context of first-aid and emergency department. No, if we consider the positive results of government campaigns in diminishing the incidence of tetanus through vaccination. And, finally, no if an openly idea-forming magazine such as RBTI has decided to promote and publish, in a partnership with AMIB, a precious guideline on this disease which is still so much a part of Brazilian reality.

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