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TETANUS - A CASE REPORT, REVIEW OF LITERATURE AND RECENT ADVANCES IN MANAGEMENT

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ABSTRACT

Tetanus remains a common infection in the poor, developing countries of the world where its mortality is still high. Intensive care unit (ICU) facilities, not readily avail-able in those countries, are required in severe tetanus for a favourable outcome. The objective of this report is to draw attention to an uncommon source of tetanus very unlikely to be covered by the existing maternal-child vaccination programme. A case of tetanus in a young woman who had induced abortion was seen and managed in Abia State University Teaching Hospital, (ABSUTH), Aba. The patient died less than 48 hours of hospitalization, prompting this review of recent advances in management of tetanus.

In conclusion, because of some uncommon and trivial sources of tetanus, expensive and scarce medications for neutralizing tetanus toxins, availability of cheap and ef-fective vaccine, high mortality associated with severe tetanus and the dire need for ICU facilities in severe cases, one is constrained to advocate for universal tetanus immunization with booster doses as the need arises.

Key words: tetanus–recent advances in management of tetanus–universal tetanus immunizations–high mortality.

1 BACKGROUND

Tetanus, caused by clostridium tetani (an obligate, gram positive bacillus whose spores contaminate wounds), is associated with high mortality especially in poor countries despite availability of a cheap, safe and efficacious vaccine. Wounds leading to tetanus these days are less severe and often trivial - the serious wounds are generally given better medical attention with immunization coverage. In 15 - 30% of tetanus [1] cases, there is no evidence of a recent wound, and the source of tetanus is reported as unknown. In some others, the portal of entry of tetanus may be atypical such as infection of skin and middle ear, dental caries [2], septic abortion or intramuscular injection.

WHO focus has been on eliminating maternal, neonatal and childhood tetanus via immunizations during pregnancy. Prevention of tetanus is achievable via vaccination and good wound care. However, teenagers and young women indulging in criminal (induced) abortion are at increased risk of tetanus as they are not, routinely, given tetanus vaccine before, during or after the procedure.

A case of tetanus managed in a tertiary health facility in Nigeria is described in this report to create awareness about this source of tetanus that may not be covered by the current maternal-child immunization programme which is meant to eradicate tetanus in nursing mothers, neonates and children; and to discuss the recent advances in the management of tetanus.

Approval was obtained from the Research and Ethics committee of ABSUTH, Aba, and consent was obtained from the mother of the girl (father was late) to use her clinical details.

2 CASE REPORT

Miss F.N, a 23 year old apprentice seamstress, presented to the emergency room with recurrent body spasms and muscle rigidity, lock jaw, neck pain and stiffness for 24 hours prior to presentation. She had had an induced abortion of a 4-month pregnancy in a non hospital setting by a medically unqualified person one week before presentation. She bled per vagina heavily after the procedure and was still bleeding at presentation. There was no history of fever, headache or vomiting and no history of facial weakness, speech impairment or weakness of one side of the body.

Examination showed an acutely ill young lady who was afebrile (temperature was 37 degrees centigrade), anicteric

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but pale. She had marked trismus with rigidity of the abdominal and trunk muscles. Her pulse rate was 104 beats per minute, blood pressure 140/90mmHg with normal heart sounds. She was tachypnoeic, conscious, well oriented in time, place and person with no neurological deficits.

A diagnosis of tetanus secondary to septic abortion was made. Her management included admission in a dark quiet room, iv 5% glucose/water infusions, spasm and muscle rigidity control (using a combination of diazepam and chlorpromazine), iv metronidazole 500mg 8 hourly, intranasal oxygen and iv ceftriaxone 1gm daily. Anti tetanus serum (ATS) and Human tetanus immunoglobulin were prescribed but were not available in the facility to be administered. The patient, unfortunately, passed on less than 48 hours of hospitalization.

3 DISCUSSION

With the expanded programme on immunization, tetanus has become a disease of the developing world where 50% of deaths due to tetanus occur in neonates [3] . In the developed world, the reported incidence of tetanus is not known [4–7] In USA, risk of developing tetanus is higher in the elderly [5, 8, 9] , the immunocompromised and drug abusers [8, 10] ; these are the same population where tetanus is most fatal. In developing countries, the incidence of tetanus [11, 12] ranges between 30 -50% and it is one of the ten principal causes of death [13] . In Nigeria, tetanus is a major cause of high mortality in both young and old persons [14]

Pathogenesis: when tetanus spores contaminate a wound, the tetanus organism proliferates under anaerobic conditions and secrete two toxins - tetanolysin and tetanospasmin. Tetanolysin damages the surrounding tissues and decreases their redox potential thereby optimising the environment for the tetanus organism to multiply. Released tetanospasmin spread to the underlying tissues and attach to nerve terminals in the case of localized tetanus. In generalized tetanus, the toxins diffuse to the bloodstream from where they are carried to all tissues of the body (except the brain and spinal cord) where they attach to the nerve terminals. It does not cross the blood-brain barrier and, therefore, does not enter the central nervous system (CNS) directly. From the nerve terminals, the tetanospasmin is transported in a retrograde axonal direction to the cell body of motor nerve, cross the synapse to bind at the presynaptic inhibitory neurons in the spinal cord. This toxin inhibits the synaptic release of gamma-amino butyric acid (GABA) and glycine which are the main inhibitory neurotransmitters. Symptoms of tetanus (spasm and muscle rigidity) occur when tetanospasmin inhibits the synaptic release of GABA and glycine. The alpha- motor neurons are inhibited first before the sympathetic and parasympathetic neurons because the toxins travel faster (within 2 - 14 days) in the alpha- motor neurons. The longer pathways of the autonomic nervous system and the slower rate of toxin transport in them accounts for autonomic dysfunction occurring some days after the onset of spasm.

Loss of inhibition of the motor nerve, sympathetic and parasympathetic neurons lead to the clinical manifestation of tetanus which include muscle rigidity, spasm and autonomic dysfunction (resulting from sympathetic and parasympathetic over activity). Binding of the tetanospasmin to the alpha- motor and autonomic neurons is thought to be irreversible so that recovery requires new growth of of nerve terminals - this explains the long duration of the disease [1] .

Recent advances in tetanus management:

Principles of management [15] of tetanus include:

1. Early diagnosis by clinical features and spatula test
2. Neutralization of tetanus toxins with HTIg 500iu intramuscular (or ATS if not available)
3. Tetanus toxoid vaccination
4. Eradication of tetanus organisms using wound debridement and antibiotics (metronidazole).
5. Under general anaesthesia:
   - wound debridement,
   - tracheotomy (if dysphagia or generalized rigidity is present)
   - Nasogastric tube for feeding
6. Transfer to high dependency unit/ICU
7. Control of spasms and muscle rigidity.
8. Control of autonomic dysfunction.
9. Nutrition, general nursing, mouth and tracheotomy care.

In no specific order, a review of the recent advances in the management of tetanus is discussed below. Making a diagnosis of tetanus could be challenging even in centres with no resource limitations. This is because many young clinicians may pass through the medical school without seeing a case of tetanus and there is no laboratory diagnostic tests for it.

Treatment for tetanus, before the 60s, has been mainly symptomatic - consisting of heavy sedation and nursing in a quiet dark room to avoid external stimulation of spasm by noise and light. This is still the practice in most centres in the developing countries. The index patient in this report was managed essentially along this line. Intensive care facilities, personnel and ventilatory support are limited in the developing countries. This treatment modality has been fraught with high mortality; causes of death being early respiratory failure secondary to spasms, respiratory obstruction by secretions, aspiration, exhaustion or infection[16].

In the 1960s, muscle relaxants (to cause paralysis), artificial ventilation and intensive care (ICU) was adopted for managing severe tetanus. This led to a considerable reduction in mortality. Causes of death in the latter treatment changed from respiratory failure to cardiac causes due to marked autonomic dysfunction [16]. To date, heavy sedation, muscle paralysis and artificial ventilation have been the mainstay of treatment of tetanus. With this treatment, mortality from severe tetanus has decreased by 20 - 40% in the developed countries; mortality being dependent on the ICU facilities available [8, 17] and is from complications of treatment and cardiovascular complications from uncontrolled sympathetic over activity.

Once tetanus is established, no specific drug has been discovered which can counteract the toxin which is bound to the nervous tissue. This is the situation notwithstanding that the pathophysiology of tetanus has been explained

to the molecular level [15]. The only specific treatment for tetanus to date is eradication of the organism from the wound and neutralization of the circulating toxins in the bloodstream (especially during the incubation period). By the time clinical symptoms occur, most of the toxin has been firmly bound to the nervous tissue and cannot be accessed by the antitoxin. Parenteral antitoxin can only neutralize the toxins circulating in the bloodstream.

Intrathecal antitoxin has been given in an attempt to inactivate the toxin bound to the nervous tissues at the level of the spinal cord. This technique [8, 18, 19] has been reported to be valuable by several studies but a meta analysis failed to support use of intrathecal antitoxin in neonatal tetanus [20]. The safety of intrathecal antitoxin is not clear as there are reports of transient blindness and transverse myelitis after intrathecal administration.

Neither the equine tetanus antitoxin (ATS) nor human tetanus immunoglobulin (HTIg) has been approved for intrathecal use. In USA, ATS is formulated for intramuscular and intravenous use but HTIg is approved for intramuscular use only. Intramuscular HTIg is the antitoxin of choice with 500iu being the recommended dose. ATS is still used in many countries of the world in doses of 5000iu intramuscular and 5000iu infiltrated around the wound due to the nonavailability of HTIg . Hypersensitivity (anaphylactic) reactions are common with ATS. The USA preparation of HTIg is not filtered, contains thimerosal and aggregate of immunoglobulins while some European manufacturers produce HTIg that does not contain thimerosal. It is noteworthy that parenteral antitoxin should be administered as soon as diagnosis of tetanus is made before wound debridement in a bid to minimize toxin release during the procedure.

Eradication of the tetanus organisms is done via wound debridement under general anaesthesia and use of antibiotics. Wound debridement is most effective after initial injury before tetanus is diagnosed. Unfortunately, most wounds implicated in tetanus are so trivial that they are either ignored or treated with home remedies. It has been stated that wound debridement is useless after tetanus has been established and that antibiotics are of no value after wound debridement[1]

Penicillins, effective against most clostridial infections, used to be the antibiotics of choice for tetanus. It is no longer recommended as it is a GABA antagonist which can aggravate the spasm of tetanus [21]. Again, presence of beta lactamase producing organisms in a wound eg staphylococcus aureus and E.coli would inactivate any little penicillin that gets to the wound environment. Metronidazole is now the antibiotics of choice (given 500mg as intravenous infusion 8 hourly for 7-10 days) as it is rapidly bactericidal against the whole spectrum of obligate anaerobes. Erythromycin, tetracycline, chloramphenicol and clindamycin are accepted as alternatives to metronidazole. [22]

Prevention of early complications of tetanus is important. Pulmonary aspiration and laryngeal obstruction are common causes of mortality in moderate and severe tetanus. Aspiration in such cases results from muscle rigidity and sedation, inability to swallow saliva, pharyngeal spasms, gastric stasis and increased intrabdominal pressure during spasms. Therefore, it is recommended that once the diagnosis of moderate or severe tetanus is made, patient's airway should be protected by urgent tracheotomy before being transferred to the ICU for monitoring and care. Tracheotomy should be done within 24 hours of diagnosis, preferably before spasms start. Once the airway is isolated with a tracheal tube, feeding can be commenced without danger of aspiration. The index patient in this report did not have a tracheotomy.

Current symptomatic treatment of severe tetanus requires quality intensive care for 33 - 40 days [9, 17] with the objective of controlling spasm, rigidity and autonomic dysfunction while providing adequate ventilation, oxygen and nutrition.

Heavy sedation (almost reaching anaesthetic level) controls less severe spasms but not the severe spasms and rigidity. The sedation in the latter situations cause reduced chest compliance, therefore, creating the need for artificial ventilation. Sedatives are given in combination to control rigidity and spasms.

Benzodiazepenes and barbiturates are GABA agonists and are commonly used in tetanus, being inexpensive in the long term. Their recommended doses are: phenobarbital 240mg 8 hourly or amylobarbital 600mg over 24 hours and diazepam 15 - 100mg/ hour. Midazolam is now preferred to diazepam (which has been the more popular sedative) as it (unlike diazepam) does not cause venous thrombosis, tolerance and withdrawal symptoms. Drawback of midazolam in the developing countries is the cost. [23–25]

Chlorpromazine is used in combination with a GABA agonist and has the advantage of being an alpha blocker which is useful in suppressing sympathetic overactivity but may pose a problem in the presence of hypotensive episode.

Propofol has, also, been used in severe tetanus and is not associated with tolerance, addiction or withdrawal symptoms. It is given with a loading dose of 50mg/kg body weight followed by 3.5 - 4.5mg/kg body weight/hour infusion with no need for other sedatives. It has an added advantage of fast recovery and decreasing of muscle rigidity but it is expensive and is not known to control sympathetic overactivity.

Neuromuscular blocking agents have been used to cause muscle paralysis in severe tetanus and the commonly used ones include pancuronium and vecuronium.

Control of autonomic dysfunction in tetanus is important to achieve a favourable outcome. Basal sympathetic overactivity includes resting tachycardia, depression of bowel motility and bladder function while severe sympathetic overactivity includes fluctuating tachycardia, labile hypertension and sweating. Increased parasympathetic activity causes profuse salivation and bronchial secretions. Again, episodes of bradycardia and hypotension which often lead to cardiac arrest is attributed to increased parasympathetic activity but others believe it is due to withdrawal of sympathetic activity. Cardiac arrest in tetanus has, also, been attributed to myocardial damage caused by high catecholamine levels [26] and toxic damage to the brainstem. [27]

Alpha and beta adrenergic antagonists were recommended [28] in 1968 when cardiovascular instability in tetanus was first recognized as being due to sympathetic overactivity. Other treatment modalities for autonomic dysfunction included:heavy sedation which

controls spasms too,clonidine which has been used for sympathetic overactivity with conflicting results [29, 30]and Magnesium sulfate (MgSO4) in severe tetanus.

New agents for tetanus - tetanus has been described as a third world disease that requires first world technology to treat [31]. Intensive care facilities for ventilation and support is critical in severe tetanus. Dantrolene, a skeletal muscle relaxant, is used to control spasms in tetanus without need for artificial ventilation. It has no effect on sympathetic overactivity. Baclofen, a GABA beta agonist, is used in some centres.

Magnesium sulphate (MgSO4) is new in tetanus treatment. It has the advantage of blocking both neuromuscular transmission and sympathetic overactivity. MgSO4 inhibits the release of acetyl choline and has been shown to spare the respiratory muscles [32]. It is effective in the control of spasms and rigidity without the need for ventilatory support. It has been found to be effective in the prevention of hypertension and tachycardia in severe tetanus. With MgSO4, supportive treatment was simplified as patient was conscious and cooperative making tolerance to enteral feeding with Naso-Gastric tube possible. This helps to take care of the associated weight loss seen in tetanus which results from the increased metabolic rate characteristic of tetanus. Therefore, MgSO4 should be first line therapy in the routine management of tetanus. A loading dose bolus of 5g over 20 minutes should be followed by 3 - 4.5g per hour.

Prevention of tetanus [33] is feasible through immunization with tetanus toxoid containing vaccine (TTCV). People who recover from tetanus do not have natural immunity and can be infected again. To be protected throughout life, WHO recommends an individual should receive 6 doses of TTCV (3 primary plus 3 booster doses). The 3 primary doses start at 6 weeks after birth or on first contact with health system and 4 weeks subsequently. The 3 booster doses start at second year of life (12-23 months) or 2 years after completing the primary doses and at least 4 years between doses. WHO/UNICEF in June 2018 strongly recommended the replacement of tetanus toxoid with tetanus-diphtheria vaccine in childhood to protect against tetanus and diphtheria.

4 CONCLUSION

Drawing from the published literatures on tetanus and the fact that everyone, from the developing or developed countries, rich or poor, runs some risks of sustaining an injury some day, prevention of tetanus in all may be the way to go. With MgSO4 infusions as a first line therapy for tetanus, it is hoped that intensive care facilities and resources will soon become less critical in the management of severe tetanus. In the light of the foregoing, there is every need for a multidisciplinary team involving the physician/neurologist, anaesthetic, obstetrician, general/plastic surgeon, nutritionist, nurses and the physiotherapist in the management of moderate and severe tetanus.

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