CLOSTRIDIAL OCULAR INFECTIONS*
CASE REPORT OF GAS GANGRENE PANOPHTHALMITIS
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Introduction
THERE has been recent interest in the ophthalmological and general medical literature on the prophylactic treatment of tetanus. However, tetanus is only one disease caused by the spore-forming, Gram-positive, obligate, anaerobic rods known as the Clostridia. In addition to tetanus this group of pathogens also causes gas gangrene and botulism. The most common offenders of this species are the group causing gas gangrene. This paper presents a recent case of panophthalmitis caused by Clostridia perfringens, the commonest of these organisms. In addition, the subject of ocular clostridial infections in general is reviewed, and how they specifically affect the eye.

Case Report
Present Illness.—A 9-year-old boy was admitted to the North Carolina Baptist Hospital on March 24, 1963. Two hours before admission he was struck in the left eye by a flying object while using a hammer and chisel. Because he did not complain there was a two-hour delay in initiating treatment.

Physical Examination.—Vision in the right eye was 20/20 and in the left eye 20/200 slowly, with poor colour perception but good light projection. At the nasal aspect of the upper lid there was a linear laceration, measuring 4 mm. in length, just behind the lash margin. There was a large subconjunctival haemorrhage over the entire nasal half of the globe. The anterior chamber and cornea were grossly clear. The pupil was eccentric and ovoid from 11 o'clock to 6 o'clock and dilated to mid-position. The direct and consensual pupillary reactions were intact bilaterally, but less active in the left eye.

A small perforation of the sclera was noted at the 10.30 o'clock position about 8 mm. from the limbus. The extra-ocular movements were intact. The fundus examination revealed a posterior vitreous haemorrhage in the macular area, and a glistening metallic foreign body was easily seen in the inferior nasal quadrant in the vicinity of the equator, at the end of a vitreous tract. No bubbles were seen in the vitreous body. On slit-lamp examination the anterior chamber was deep and showed a moderate aqueous flare and cells. The lens and iris were grossly normal.

Radiographic studies were performed in the anterior-posterior, lateral, and stereo-Waters projections, and confirmed the presence of a metallic intra-ocular foreign object measuring 5 × 1 mm.

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Course in Hospital.—The patient's pupil was widely dilated. He was given tetanus toxoid and a course of systemic chloromycetin and aqueous and procaine penicillin was begun.

At 6 p.m. he was operated on and the metallic foreign body was removed with a hand magnet without difficulty. Post-operatively, the antibiotics were continued in full therapeutic doses.

On the morning of March 26 when the dressing was changed it was noted that the patient was lethargic and appeared to be acutely ill. His temperature was 102·6° F.; the night before it had been 100° F. orally and he had been comfortable.

Examination of the eye at this time revealed a fulminating panophthalmitis. The lids were erythematous and almost swollen shut, with a brawny non-crepitous oedema which extended slightly beyond the orbital rim (Fig. 1). The bulbar and tarsal conjunctiva and episclera were diffusely injected. The cornea was oedematous, and the anterior chamber was filled with a non-haemorrhagic viscous yellow exudate. There were no visible gas bubbles. The entire iris was obscured (Fig. 2).

The white blood count rose from 8,100 on admission to 15,000 on March 26 with a marked shift to the left. Smears taken at the time of operation revealed Gram-positive cocci and bacilli. The cultures grew haemolytic Staphylococcus aureus, coagulase negative, which was sensitive to penicillin and chloromycetin. Smears and cultures of the exudate as well as blood cultures were taken for general and anaerobic culture on March 26. Strict isolation technique was then instituted and the patient was placed on a continuous intravenous drip of chloromycetin and aqueous penicillin.

On March 27 an anaerobic rod was grown on blood agar which was an excellent gas former. The smear revealed Gram-positive bacilli.

The condition of the patient on March 27 and 28 was essentially unchanged except for a slight increase in proptosis and corneal oedema, with a horizontal ridge in the cornea from lid pressure. In view of the patient's lack of response to therapy it was decided to perform an evisceration of the globe on the afternoon of March 28.

By 2 o'clock on March 29 his temperature was 100·4° F. rectally and he was alert, comfortable, and sitting up in bed eating a full meal. The dressing was changed and moderate drainage only was observed on the dressing and in the operative site. There was very little resorption of the
peri-orbital oedema. The patient was afebrile on March 30 and remained so for the rest of his stay in hospital. At that time the swelling was minimal, and there was no significant discharge from the operative site.

Culture specimens sent to the Communicable Disease Control Center in Atlanta confirmed the laboratory report of Clostridium perfringens. The pathology report was also consistent with an acute bacterial inflammatory process in disorganized ocular contents. Gram stains of the contents of the globe and the cornea revealed many Gram-positive bacilli.

Six weeks post-operatively the patient was able to wear a stock prosthesis which was cosmetically acceptable.

**Discussion**

It is noteworthy that even before the widespread use of tetanus antitoxin or toxoid the incidence of reported eye infections from Cl. tetani infections was rarer than infections from the clostridial group causing gas gangrene.

**Identification**

The Clostridia (Harrison, 1954; Sussman, 1958; and Jawetz, Melnick, and Adelburg, 1960) are an extremely common and widespread group of organisms, whose natural reservoir is the soil or the intestinal tract of animals and man; the majority are saprophytic organisms in the soil. Effective control over the reservoir of these organisms is not now possible, as was medical science's attack on the reservoirs of yellow fever and malaria.

The Clostridia may be broken down into roughly three groups clinically. They all vary in their ability to break down proteins and produce toxins. They are Cl. botulinum, causing botulism, Cl. tetani, causing tetanus, and several types of Clostridia causing gas gangrene—commonly Cl. perfringens, Cl. novyi, Cl. septicum, Cl. histolyticum, and Cl. fallax. As a rule, in infections caused by these clostridia, other non-toxigenic clostridia organisms, such as Cl. bifermentans and Cl. sporogenes, are frequently found as well as various cocci causing a mixed infection. All the clostridia organisms are large, rod-like organisms with a larger spore-forming end giving them a drumstick appearance.

The diagnostic identification of Cl. tetani and the clostridia causing gas gangrene differs. All the clostridia grow only in an anaerobic environment. There are some characteristic features when they are seen in colonies. Most of this species will produce a zone of haemolysis on blood agar media. On agar plates Cl. tetani forms small colonies which send out fine filamentous projections.

Tetanus (Harrison, 1954; Jawetz, Melnick, and Adelburg, 1960) has been a clinical entity mentioned in the earliest records. There is even a suggestion of it in Hippocrates (Sussman, 1958). Experimental work by Nicolaier in 1884 (Drew, 1954) demonstrated that the responsible agent for tetanus was a Clostridia organism. Identification of Cl. tetani depends on the production of a heat-labile protein toxin by the organism and the neutralization by a specific antitoxin. If the toxin is heated for 5 minutes at 65° C., it is inactivated and destroyed by proteolytic enzymes. At least ten antigenic types have been isolated, but all have immunologically identical exotoxins.

The clostridia which produce gas gangrene produce a variety of toxins. These toxins all have haemolytic, necrotizing, and lethal properties to varying degrees. The most common member of this group of organisms is Cl. perfringens (Cl. welchii).
This organism was identified by the work of Welch and Nuttall in 1892. Some examples of the exotoxins produced by the Cl. perfringens are the theta and alpha toxins which vary in their haemolytic and necrotizing properties and whether they are lecithenases or not. This last-mentioned property is important since in man the cell wall is made up of a lipoprotein. There are at least twelve such toxins identified to date. The Cl. novyi has eight, the Cl. histolyticum five, and the Cl. septicum five exotoxins identified. The different gas-gangrene producing Clostridia may be differentiated by their biochemical reactions in the fermentation of certain sugars and in their reaction in litmus milk, Loeffler's serum, iron gelatin, and the Nagler test. Final differentiation will depend on their neutralization by a known specific antitoxin to the toxin produced by a specific organism. Since Cl. perfringens is the most common organism in the ophthalmological literature to cause gas gangrene, we will limit our discussion of the appearance on blood agar to that one organism. Typical Cl. perfringens colonies are about 3 mm. in diameter and surrounded by one or more rings of varying degrees of beta haemolysis due to several types of haemotoxins. Clostridia are called "facultative pathogens" because not all contact with this pathogen causes disease. It requires special conditions in order to produce disease. The most important prerequisite is a capacity of the tissue infected to have a lowered oxidation-reduction capacity.

The eye is a unique structure with its avascular lens and vitreous. Add to this the fact that wounds of the eye cannot be widely débrided and left open and we have an ideal situation for the growth of the Clostridia organism. As pointed out by MacLennan (1962), this lowering of oxidation is aided by the presence of foreign bodies, decrease in blood supply to the area, and the presence of necrotic tissue and haemorrhage. As a result of this lower oxygen concentration, the pyruvate in tissues is reduced to lactate and the pH falls. This in turn increases enzymatic proteolytic activity releasing amino-acids locally, and produces those special conditions for the growth of the Clostridia organism.

The distribution, reservoir, growth characteristics, and morphology of Cl. botulinum (Harrison, 1954; Jawetz, Melnick, and Adelburg, 1960) is similar to the other Clostridia. The different types can be separated by the antigenic reaction of the toxins. The toxins affecting man are types A, B, C, D, and E. Types C and D cause limber neck in fowl and botulism in cattle respectively. The site of action of these toxins is at the neuromuscular junction with the blockade of acetylcholine.

Clinical Signs and Symptoms

In Leavelle's (1955) extensive review of the literature he lists the following four common characteristics for gas gangrene panophthalmitis: (1) the infection follows a perforating wound; (2) vision is lost despite all treatment; (3) the cases ended in either evisceration or enucleation; (4) the post-operative recovery was uneventful. Our case certainly does not deviate from these criteria.

The clinical picture (Duke-Elder, 1940; Cross, 1941; and Fedukowicz, 1963) is one of severe pain with rapid loss of vision and an extensive panophthalmitis with chemosis of the conjunctiva and brawny swelling of the lids. The case reported here shows this, as can be readily seen in Fig. 1. The oedema of the lids, as is frequently the case, is limited to the peri-orbital tissues. The rise in intra-ocular
pressure, although evident by digital examination, could not be measured accurately. Fig. 2 shows a hypopyon without gross gas bubbles or a coffee-coloured appearance to the exudate, such as is frequently described; other features occurred, such as loss of light perception and loss of the fundus reflex, as well as severe limitation of movement of the globe, as may be expected from Fig. 2. The clinical course of our patient’s symptoms and the laboratory findings and his response to treatment make his case a typical example. A feature which is often described but which this patient did not show was a ring abscess. Neither did he show gross clinical evidence of gas formation which is so characteristic of Cl. perfringens, but which may be absent in infections due to Cl. noyvi and Cl. bifermantans.

The presence or absence of gas may be misleading. As we have noted above, some of the organisms causing gas gangrene do not produce gas as a rule. On the other hand, there are other organisms such as Escherichia coli, anaerobic streptococcus, and bacteroides which produce some gas and may be mistaken for gas-forming Clostridia. Gangrene secondary to these other organisms is not a common condition, and when it is found it is usually in a diabetic. The E. coli, for instance, will produce gas more readily in the presence of increased dextrose. It is important to differentiate this group from the Clostridia, since therapy differs in the two groups. In the cases of this type presented and reviewed by Spring and Kahn (1951) there were no reported cases involving the globe or adnexa.

Another unusual form of Clostridia welchii infection recently reported by Henkind and Fedukowicz (1963) was a primary conjunctivitis unrelated to trauma.

The organisms in vitro are usually sensitive to broad-spectrum antibiotics. However, these are usually ineffective and evisceration is resorted to with excellent results. Several places in the United States are apparently successfully treating gas gangrene of other parts of the body with hyperbaric chambers.

Tetanus infections, as mentioned before, are extremely rare. In a review by Wetzel in 1942, there had been reported only 30 cases of tetanus related to eye injuries up to that time. Half of these cases were reported as developing a panophthalmitis with no particular distinguishing features. Some of the cases developed marked supputation. This was believed to be caused by other bacteria, since Cl. tetani in other types of wounds frequently does not suppurate. The usual eye infections due to Cl. tetani or botulinum are usually secondary to the systemic disease. On the other hand, Tsutsui (1957) reported one case of primary tetanus infection of the cornea.

The chief characteristic (Walsh, 1957a) of cephalic tetanus is recurring muscular spasm and generalized rigidity. This muscular spasm is usually seen first in the facial muscles. As a result we see blepharospasm frequently as an early sign. Ptosis has also been mentioned, but this is probably due to the tonic muscular contraction of the orbicularis. The same is probably the explanation of the apparent extra-ocular muscle palsies.

Skudder and McCarroll (1964), in their recent review of tetanus control, advocate the use of human tetanus-immune globulin instead of equine or bovine antitoxin. They feel it is more efficacious and less likely to cause sensitivity reactions. They also follow the time-honoured principle of adequate débridement of devitalized tissue and removal of foreign bodies as a still necessary part of adequate therapy. These
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are not always easily attained in ocular injuries. The treatment with antitoxin is not without its local eye complications. One of these reported cases resulted in a secondary lateral rectus palsy which subsequently cleared (Montanelli, 1958).

In reviewing the ophthalmic literature, no reported cases of primary ocular botulism were found. However, eye signs are prominent in systemic botulism (Walsh 1957b).

An early sign is a dilated pupil which reacts poorly to light. Blockade of accommodation is another well-known ocular sign. The other extra-ocular muscles and the levator may be affected, resulting in diplopia and ptosis.

The treatment for botulism is the administration of polyvalent botulinus antitoxin.

Summary

A case of panophthalmitis due to Cl. perfringens is reported and primary ocular Clostridia infections are reviewed. The signs, symptoms, treatment, and diagnostic features of identification are discussed. Our results in treating this case, despite newer antibacterial agents, did not alter the inevitable outcome pointed out in previously reported cases. Several newer theories of treatment are discussed and others noted as holding out a ray of hope in future cases.

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Clostridial ocular infections. Case report of gas gangrene panophthalmitis.

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