Carrion’s disease

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History

South American-bartonellosis, (Carrión’s disease, Oroya fever, verruga peruana, verruga peruviana) results from infection with the bacterium *Bartonella bacilliformis* and is transmitted by **sandflies**. The infection manifests itself in **two very different clinical forms** with the causal connection being recognised by the young Peruvian doctor Daniel Alcides Carrión.

Pre-Columbian mummies with histologically confirmed verruga lesions have been discovered in Peru and bartonellosis occurred in Francisco Pizarro’s army (1471-1541). During the Inca era, the disease was called “Sirki,” which means “warts in blood.” In Peru between 1869 and 1873 more than 7000 workers building the Lima-La Oroya railway died from the disease at Cocachacra, 65 kilometers from Lima, 1600 meters above sea level. The name “Oroya fever” refers to this, although in the mining town of La Oroya (altitude 3800 m), strangely enough there was no transmission of Oroya fever. In 1936 a large epidemic was seen in the Guaitara valley on the border between Colombia and Ecuador. An epidemic occurred in 1980 in Ecuador and another in 1987 in Peru with a death rate of 88% in the untreated patients. Now and then there have been isolated cases or small outbreaks. In 1997 there was an outbreak in the area of Cuzco, Peru. In an outbreak in Zumba, Ecuador (1995-96), large numbers of dead rodents were found around the places where the cases had occurred. This finding led to the hypothesis that bartonellosis could have an animal reservoir.

Daniel Alcides Carrión

Daniel Alcides Carrión (1858-1885) was a medical student in Lima, Peru. He was required to prepare an original thesis and choose to study the epidemiology and clinical manifestations of verruga peruviana. His home was in Cerro de Pasco, a mining town high in the Andes where he had seen many cases. These left a deep impression on the young man. He told a classmate that he hoped “to make an important contribution to aching humanity”. He became concerned with the difficulty in diagnosing verruga peruviana before the typical eruption started. The appearance of the skin lesions was preceded by fever and anaemia, but there was a lot of confusion between the prodromal phase of verruga and other febrile disorders such as malaria. Carrión wanted to determine the incubation period and early symptoms of verruga, so he decided to inoculate himself with some fluid from a chronic skin lesion of a verruga patient. Many friends and professors tried to dissuade him. On the morning of August 27, 1885, Carrión was in the Nuestra Senora de

las Mercedes ward of the Dos de Mayo Hospital in Lima. A 14-year-old boy named Carmen Paredes was admitted with verruga on his right eyebrow. Assisted by Dr Chavez, a young ward physician, Carrión used a lancet to inoculate his own arm with blood taken from that verruga. He kept a diary afterwards. The first symptoms started after 21 days, with discomfort and pain in his left ankle. Two days later he developed fever, chills, abdominal pain and generalised pain in bones and joints. He had anorexia and noted severe thirst. His urine became dark red and scanty. He developed jaundice. A week later, he became too ill to continue his diary. His classmates took over this task and were surprised at how quickly anaemia developed. A systolic heart murmur developed and grew in intensity. A few days later, muscle fasciculations appeared in his arm muscles. He said to his friends: “Up to today, I thought I was only in the invasive stage of the verruga as a consequence of my inoculation, that is, in the period of anaemia that precedes the eruption. But now I am deeply convinced that I am suffering from the fever that killed our friend, Orihuela. Therefore, this is the evident proof that Oroya fever and the verruga have the same origin, as Dr Alarco once said.” This insight was the essence of Carrión’s experiment. He had not set out to prove the single cause of verruga peruviana and Oroya fever. He only intended to study the incubation period and prodrome of verruga. When a completely different disease developed, he was lucid enough to understand the full meaning of his experiment. On October 3, he became delirious and two days later he fell into a coma and died at midday. He became a hero of Peruvian medicine and is remembered to this day. The day of his death, October 5, is celebrated yearly as the “Dia de la Medicina Peruana”. The Peruvian National University in Cerro de Pasco carries his name.


PTE. VERRUGAS
CARGA MAXIMA 60 TNS.
LONGITUD 21 m.
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Ponte verrugas in the Andes, a railway bridge on the trail Lima – La Oroya (Peru). The name refers to a bartonellosis epidemic in 1869-1873. Copyright ITM

Picture of Dr Daniel Alcides Carrion, on the road Lima – La Oroya. In this area of the Western Andes in Peru, there was a bartonellosis epidemic in 1869-1873. The disease is also known as Oroya fever or Carrion’s disease. Photo Dr Van den Enden. Copyright ITM

Aetiology

Barton described the pathogen in 1909, but he thought that it was a protozoon. The Japanese bacteriologist Hideyo Noguchi demonstrated the bacterial nature of the pathogen. *Bartonella bacilliformis* is a **small Gram-negative coccobacillus** (0.6-1 µm), which takes Giemsa and Warthin-Starry stain. The pathogen has one or more polar flagella. It replicates within the vascular endothelium and erythrocytes. The bacterium is **related to rickettsiae**. The bacillus grows quickly (extracellularly) on non-living culture media with blood or on chicken embryos at 25-28°C. Numerous

related organisms are animal pathogens.

Distribution

The disease caused by *Bartonella bacilliformis* **only occurs in certain narrow high valleys of the western-most slopes of the Andes at altitudes between 500 and 3200 meters in Peru, Ecuador and Colombia**, between 2° N and 13° S. Whether endemic cases occurred in Chili, Bolivia, Guatemala and Honduras is very doubtful. Sporadic cases of so-called “bartonelloses” have been reported in Africa, (Niger, Sudan), in Asia (Pakistan) and in the USA, but it is still not clear whether there is a connection with Carrión’s disease. Our knowledge about *Bartonella* and related bacteria has largely increased in recent years but is still very incomplete.

Transmission

A sandfly, *Lutzomyia verrucarum*, and perhaps a few related species, is responsible for transmission. Transmission only occurs at night and is seasonal, particularly during the rains. It was formerly assumed that the **reservoir was purely human, but this was recently cast into doubt** (there may be a rodent reservoir). In some of the inhabitants in the endemic valleys bacteria can be found in the blood, but these carriers are usually without any symptoms. These **latent infections** which are likely to have been contracted in childhood probably give **stable immunity**. It is only if non-immune populations enter the endemic area that epidemics occur, sometimes on a large scale, such as in wars or when large public works are being carried out. Tourists may be at risk for the disease.

Clinical aspects

The **clinical range is wide**, going from **asymptomatic infections** via serious febrile forms with acute **haemolytic anaemia**, to the **angiomatous skin lesions** which can be present from the onset or can be preceded by the febrile stage. The mortality of untreated cases varies between epidemics and ranges from 10-40% after 2-3 weeks. The disease is less severe in children and the mortality is far lower. If the course of the disease is favourable, the **fever can last for 3 to 4 months**. In 40-50% of cases of Oroya fever, **concurrent salmonellosis** (generally Salmonella typhimurium) complicates the illness and makes the prognosis less favourable. The superinfection causes fever with gastrointestinal symptoms and a deterioration of the patient’s general condition.

Acute stage or Oroya fever

1. Incubation takes approximately **3 to 8 weeks** (range 10-210 days). It begins insidiously with:

2. Irregular **intermittent febrile** attacks with shivering

3. Rapidly worsening **anaemia** with tachycardia, pallor and (sub)icterus

4. Severe **headache** with bone and joint pain. This may persist after the fever has ended

5. Enlargement of the **liver and spleen**, slightly painful on palpation

6. Generalised painful **swollen lymph nodes**

7. Myocarditis, pulmonary oedema and anasarca (generalised oedema)

8. **Haemorrhagic diathesis** as a result of the endothelial lesions: petechiae and tendency to thrombosis. Necrotic foci are found in the liver, spleen and bone marrow.

9. **Neutrophilia**

10. Spontaneous abortion, foetal death or transplacental transmission can occur.

11. **Neurobartonellosis** due to involvement of the CNS takes the form of meningo-encephalitis with or without convulsions and with high mortality. Myelitis also occurs with spastic or flaccid paraplegia with sequelae which can be permanent. There is pleiocytosis of the CSF. More focal and transient lesions of the spinal cord or of the cranial nerves are seen at the verruga stage.

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