Clinical Features of Noma: A systematic Review and Meta-Analysis of case reports

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Authors

Paola Díaz[1] pdiaz.15@alumni.unav.es

Marta Ribes[2] marta.ribes@isglobal.org

Carlos Chaccour[1,2] cchaccour@unav.es

[1] Universidad de Navarra. Pamplona, Spain

[2] ISGlobal, Barcelona Institute for Global Health. Barcelona, Spain

List of abbreviations

ANG Acute Necrotizing Gingivitis
MSF Doctors Without Borders
WHO World Health Organization

Table of content

1. Summary

Noma is a neglected disease with various important knowledge gaps, like its incidence or its etiology. Most scientific publications are case series or case reports. In this review, we intend to summarize the clinical features presented in these reports and conduct a meta-analysis on the frequency of symptoms and their mean time progression, as well as demographic factors affecting them.

2. Introduction

2.1 Background

Noma (cancrum oris) is a rapidly progressive gangrenous infection that affects mainly the oral cavity of children living in bad hygiene conditions and suffering from malnutrition and often other debilitating diseases. When left untreated, it can lead to severe soft and hard tissue destruction in the face and is associated with high morbidity and mortality [1].

The word “noma” to describe this disease was first used by Dutch surgeon Cornelis van de Voorde in 1680. It comes from the Greek and its translation is understood as “to devour”. The disease has had several names along the history but the most commonly used are “noma” and “cancrum Oris”; the latter meaning “mouth cancer” which is a confusing translation of “mouth canker”; a popular name of noma in Great Britain [2].

In the 1800’s cases were mainly reported in Europe and India; then in the 1900’s there was a shift towards Africa and North America. The disease virtually disappeared from Eruope after the Industrial Revolution only to be seen again during the First and the Second World War in Belsen and Auschwitz concentration camps and in the general population from The Netherlands due to the post war famine and poor conditions [3].

Nowadays, most noma cases are reported in West Africa, specially in Nigeria, southern Niger, eastern Burkina Faso, Mali, and Togo. This geographic proximity led to the coining of the term the “noma belt”. However the number of cases reported correlates with the amount of published literature per country and the focus of action of NGO’s such as Médecins Sans Frontières (MSF) which makes it difficult to estimate the accurate global burden of the disease. In the last few years, the reporting of cases in Southeast Asia and Latin America have increased [4].

The etiology of noma remains uncertain. There is a general consensus that it is probably caused by a bacterial infection of various genre in the presence of several risk factors such as: age from 2-5 years, malnutrition and comorbidities (HIV, malaria, measles, respiratory diseases, diarrhea); low vitamin A and C levels, poor oral hygiene, lack of access to basic health care and low socioeconomic status; among others [3].

Clinically, noma starts as a simple gingivitis, it is in this stage where prevention with oral hygiene and nutritional support is most useful. It then evolves to an acute necrotizing gingivitis (ANG) (which corresponds to WHO stage 1) and further to edema (stage 2). Up to Stage 2, the condition is completely treatable with common antibiotics, usually amoxicillin

and metronidazole. If left treated, noma progresses rapidly, within a few weeks, to a gangrene stage (stage 3) at this point it requires oral hygiene, further antibiotic treatment, nutritional support as well as open wound care [3]. The survivors can develop stage 4 disease which consists of a scarring period [5].

When left untreated during the acute stages noma has been reported to have a 90% mortality [5]. Most patients that survive these stages develop severe sequelaes (stage 5), which can involve trismus, and inability to eat or speak. These may require various reconstructive surgeries and intensive physiotherapy to improve structural and functional defects. These sequelaes often lead to social isolation and stigmatization [3].

Some of the key current knowledge gaps of noma are: the real global burden of disease, the pathophysiology, the role of the different risk factors and comorbidities and the long-term prognostic factors [3].

Often called “the neglected among the neglected”, noma disease receives very limited attention from most governments and international organizations. In the last decades, almost solely NGOs have been providing prevention and management services for this disease. There has been strong advocacy for noma to be included in the WHO list of Neglected tropical Diseases [3].

For the improvement of prevention it is important to be able to identify the disease in its different stages. No systematic review on the clinical features of noma has been conducted to date, we consider this work may help develop further prevention methods and ultimately reduce the burden of noma in vulnerable populations.

2.2 Aim

To provide an evidence-based guide on the clinical features of noma

2.3 Primary research question

What are the main clinical features of noma included in case reports available in the literature?

2.4 Specific objectives

a) To review the clinical features of noma reported in the literature
b) To determine the frequency of each symptom/sign
c) To seek potential associations between clinical features and the reported demographic characteristics
d) To review the time of progression along the Stages
e) To describe the characteristics associated with Stage progression
f) To create a public database of the clinical images already published

3. Methods

3.1 Registration

This review will be registered in PROSPERO, an International prospective register of systematic reviews.

3.2 Search strategy

Two researches (PD and MR) will perform independent searches without language or date restriction in the following databases:

- MEDLINE (via pubmed)
- SCOPUS
- Google scholar
- The archive of the Lancet
- The archive of the Royal society

Additionally, we will perform manual searches of the references in the published reports and contact the authors for clarification or additional data. If additional cases or case series are obtained through this method, and there is appropriate clinical description, these will also be included in the review.

Search terms will include:

"Noma OR cancrum oris OR necrotizing gingivitis OR acute necrotizing ulcerative gingivitis OR ANUG OR wasserkrebs OR Vincent stomatitis or Trench mouth OR necrotizing stomatitis OR fusospirochaetal gangrene OR Stomatitis gangrenosa"

3.3 Eligibility criteria and selection

We will include case reports and case series
Screening will be based in title/abstract. Efforts will be made to retrieve additional relevant data from authors.

3.4 Data collection

Data will be extracted independently and blinded by two authors using predefined, standardized, online forms.

3.5 Data Items

a) Population
Patients of any age with confirmed or suspected noma or necrotizing gingivitis/stomatitis

b) Phenomenon of interest/Intervention

Confirmed or suspected noma or necrotizing gingivitis/stomatitis as assessed by the care provider and reported in the literature with or without treatment

c) Design/Comparison
Case report or case series

d) Outcome
- Clinical features
- Staging
- Demographic characteristics
- Sequelae
- Mortality
- Images

3.6 Risk of bias in individual studies

The quality of case reports and case series will be assessed following the methodology:

- All case reports will be assessed for completion against the 13-items CARE guidelines and scored accordingly [6]
- All case reports and case series will be assessed for quality following the methodology proposed by [7].

3.7 Summary measures and result synthesis

We will generate a narrative synthesis of key and ancillary clinical features of noma and summarize potential risk factors for disease appearance, progression and outcome as well as treatment approaches. Additionally, we will create a repository of images of cases associated with their time since symptom onset.

3.8 Risk of bias across studies

Studies with a suspect of noma will be included in the report and likelihood of diagnosis based on the available data will be assessed and discussed.

3.9 Additional analyses

Regression analysis of key clinical features and potential risk factors (when available) will be conducted, the latter include:
- Age
- Stage at care seeking
- Geographic location
- Nutritional status
- Concomitant diagnoses

4. Presentation of results

4.1 Study selection

A flow diagram will be used to report numbers of studies screened, assessed and included. The reasons for exclusion at each stage will be detailed.

4.2 Individual report characteristics

Here we provide the definition and provide details of the key variables to be collected:

Age at onset: this will be defined as age in years (plus months if available) at first clinic visit.

Previous recent infections: this will include any infection in the three months preceding the onset. Collection will be done categorically (yes/no/unknown) and specification of each confirmed or suspected infection.

Immune compromise: this will include any potential cause. Collection will be done categorically (yes/no/unknown) and specification of each confirmed or suspected infection.

Access to medical care: this will be defined as access to any level of medical care within the national system (including community health workers) in a radius of less than 15 km from home. Collection will be done categorically (yes/no/unknown) and specification of the level available.

Concomitant diseases: this will include any suspected or confirmed diseases at the moment of noma diagnosis. Collection will be done categorically (yes/no/unknown) and specification of each confirmed or suspected disease.

Symptoms: each reported symptom will be recorded individually as a categorical variable (yes/no/not reported) as well as their time of onset relative to disease onset.

Noma stage: we will use the stage calculated by the report and estimate our own using the WHO scale [5] if the data is available.

Sequelae: will be defined as healed tissue with scarring and disfigurement [5].

Microbiological tests: the results of cultures will be collected as a categorical variable (yes/no/not reported) and specification of each result received.

Laboratory tests: the results of blood counts, biochemistry and or coagulation tests will be collected as a categorical variable (yes/no/not reported) and specification of each individual result received.

Treatment: the medical treatment received will be collected as a categorical variable (yes/no/not reported) and specification of each individual drug given.

Surgery: the surgical treatment received will be collected as a categorical variable (yes/no/not reported) and specification of each surgery and timing recorded.

Quality assessment: completion will be assessed with CARE's 13-items and quality with Murad's methodology [7].

4.3 Analysis

A descriptive analysis of clinical features and disease progression will be produced. Histograms will be used to illustrate the most frequent symptoms, signs and comorbidities.

We will conduct a quantitative analysis of the prevalence of clinical features. Proportions will be pooled using a random effect model. In case of extreme proportions approaching 0 or 1, we will transform the prevalence using the Freeman-Tukey double arcsine transformation [8] before conducting the meta-analysis and then transform the estimate back to a proportion.

Regression analysis of key clinical features and potential risk factors as described in section 3.9

4.3 Presentation

A comparison of results to existing scoping reviews [4] on noma epidemiology is intended.

5. Intended timeframe

	2023											
	J	F	M	A	J	J	A	S	O	N	D	J
Review team assembly												
Protocol development and registration												
Preparation of standardized forms												
Pilot search												
Validation of forms												
Full search												
Data extraction												
Quality assessment												
Meta analysis												
Manuscript preparation												
Dissemination												

6. References

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