

WORLD HEALTH ORGANIZATION
REGIONAL OFFICE FOR EUROPE

WELTGESUNDHEITSORGANISATION
REGIONALBÜRO FÜR EUROPA



ORGANISATION MONDIALE DE LA SANTÉ
BUREAU RÉGIONAL DE L'EUROPE

ВСЕМИРНАЯ ОРГАНИЗАЦИЯ ЗДРАВООХРАНЕНИЯ
ЕВРОПЕЙСКОЕ РЕГИОНАЛЬНОЕ БЮРО

32567

EUR/SPA/PCS 010/B(S)
1204B
ORIGINAL: ENGLISH

SUMMARY REPORT



Third Meeting of the WHO Scientific Steering Committee for the Toxic Oil Syndrome

Copenhagen
3-4 May 1990

1990

EUR/HFA target 19

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TARGET 19

Monitoring, assessment and control of risks in the environment

By 1990, all Member States should have adequate machinery for the monitoring, assessment and control of environmental hazards which pose a threat to human health, including potentially toxic chemicals, radiation, harmful consumer goods and biological agents.

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Introduction

The toxic oil syndrome, a new disease that appeared in epidemic proportions in Spain in 1981, affected more than 20 000 people, of whom several hundred died within the first year. The disease is chronic, with no known cure for those afflicted. The evidence points overwhelmingly to the ingestion of adulterated rapeseed oil sold illicitly as cooking oil as the cause, but the precise etiological agent or agents have not been identified with certainty.

To permit a better understanding of the mechanisms and development of the disease, the WHO Regional Office for Europe and the Social Security Health Research Fund (Fondo de Investigacion Sanitaria) (FIS) of Spain have coordinated an extensive research programme, conducted under the general guidance of the WHO Scientific Steering Committee for the Toxic Oil Syndrome. Studies have focused on epidemiology, clinical aspects of the syndrome, pathology, immunology, and analytical and experimental toxicology.

The Third Meeting of the Steering Committee was convened to review and assess the research programme and to determine the most appropriate strategy or strategies for further investigations. Five review papers covering all known studies on the toxic oil syndrome, as well as the results of 27 studies funded by the WHO/FIS research programme, formed the basis for discussion. In addition, the 23 participants were asked to evaluate the possible implications of the newly recognized eosinophilia-myalgia syndrome in terms of its etiological, clinical and pathological similarities to the toxic oil syndrome.

Discussion

Epidemiology

A clear-cut dose-response relationship was found between the level of aniline/anilide contamination of oil and the risk of a family being afflicted with the toxic oil syndrome. Follow-up studies on victims are under way to assess morbidity and mortality in the cohort and to define further the evolutionary pattern or patterns, including possible delayed effects, of the disease. Gathering of and access to data from various sources are still priority needs.

Clinical aspects

Three phases have been distinguished. The acute phase was dominated by eosinophilia, pulmonary oedema, myalgias, fever and rash. The dominant features of the intermediate phase are myalgias, weight loss, hepatopathy and sicca syndrome. In the chronic phase, major clinical findings are peripheral neuropathy, hepatopathy, scleroderma and pulmonary hypertension. After eight years, most of the survivors are showing progressive clinical improvement. Nevertheless, new cases of pulmonary hypertension, chronic hepatitis and hyperglycaemia still appear.

Except for corticosteroids used to treat the eosinophilia, no particular treatment has been effective. In the chronic phase, rehabilitation therapy has been helpful.

Pathology

The fundamental lesion was vascular, with swelling and a subsequent inflammatory infiltrate in the vessel wall. This lesion probably underlies all of the end-organ pathology of the toxic oil syndrome. The first organ to be severely affected was the lung. In the chronic phase, skin and nerves are affected. The pulmonary lesions of the chronic phase are similar to those seen in primary pulmonary hypertension. Intimal proliferation, hypertrophy of the media and thromboembolism are seen in pulmonary vessels. Nonspecific inflammation, cholestatic hepatitis, nodular regenerative hyperplasia and frank cirrhosis have been seen. In the chronic phase, fibrosis of salivary glands has been seen in association with sicca syndrome.

The lack of systematic or comprehensive arrangements for autopsies of victims may mean that some cases have not been autopsied.

Immunology

Immunologically, the disease appears to have an early and late phase, which may involve more than one mechanism. The early phase is marked by hypereosinophilia and, frequently, high levels of immunoglobulin E, pointing to an immediate hypersensitivity reaction. The late phase appears to be marked more by a chronic and primarily mononuclear response. As with graft-versus-host reactions, which lead to auto-antibody formation, auto-antibodies have been seen in victims. Research into the mechanisms of hypersensitivity and auto-antibody formation would be desirable.

Experimental toxicology

Most toxicity studies have yielded negative results. However, doubts have been raised about whether the oil samples used in many of these studies came from authentic case-related oils and whether the lesions noted were related to the etiological agent of the toxic oil syndrome or were the result of an experimental artefact. All more recent toxicological studies done in an appropriate way and with oils authenticated to be case-related have yielded negative results. These findings suggest that either the etiological agent shows species specificity or it has decreased in concentration over time.

Analytical toxicology

A major difficulty in the chemical analysis of case-related oils is that they contain many compounds. These compounds include not only fatty-acid anilides but also reaction products of aniline and triglycerides. In addition, pure aniline, after heating, will form still other compounds.

The only substances that currently can be shown to have a sound epidemiological association with the illness, for which there is analytical evidence of their presence in case-related oils and which are reasonably stable over time, are the anilides of oleic, linoleic and linolenic acids. Furthermore, the results of the toxico-epidemiological studies completed to date show fatty-acid anilides as the only accepted biomarkers for identifying case-related oils.

Another major difficulty is the lack of an animal model; to date, the disease has not been reproduced in any laboratory animal tested.

Eosinophilia-myalgia syndrome

This new syndrome bears certain clinical similarities to those of the toxic oil syndrome, including intense eosinophilia, the morphology of the vascular lesion, axonal neuropathy, sclerodermiform skin lesions and pulmonary hypertension. It is associated with the ingestion of L-tryptophan, an amino acid long used as a dietary supplement. As with the toxic oil syndrome, the specific etiological agent for the eosinophilia-myalgia syndrome is currently unknown, but contamination during processing is suspected. Some 1500 cases, including 20 deaths, have been reported in the United States, 90 cases in the Federal Republic of Germany and one case in the United Kingdom. Investigation into the clinical, pathological, immunological and chemical similarities between the two syndromes would be desirable.

Conclusions

General

1. The research programme needs to focus on the outstanding problems as identified at this meeting. To meet this need, selected research groups will be invited to apply for funding to carry out specific projects. Where necessary, an international call for qualified groups to submit research proposals on such projects will be made.
2. Similarities between the toxic oil syndrome and the eosinophilia-myalgia syndrome warrant closer collaboration between researchers involved in either disease. An exchange of information between the WHO Regional Office for Europe and the US Centers for Disease Control on the toxic oil syndrome and the eosinophilia-myalgia syndrome would be desirable.

Epidemiology

3. Data-gathering is hampered by a lack of coordination between physicians caring for patients with the toxic oil syndrome and investigators of the disease. In addition, data needed for generating statistics on morbidity and mortality are not accessible to researchers because of right-of-privacy legislation.
4. Considering the chronic nature of the disease, a number of follow-up studies focusing on different aspects of the disease would be desirable.
5. Post-mortem examinations of victims are not done routinely, and coordination between the many pathology and forensic medicine departments at various hospitals is needed.

Pathology

6. Further research will depend on identification of and access to adequately prepared specimens from autopsied victims. This research is hampered by an incomplete inventory of autopsied material.

Immunology

7. No direct evidence has been found for the immunological mechanisms thought to be involved in the toxic oil syndrome. An immunological basis of the disease will be very difficult to establish without an in vitro or in vivo

model. A more useful approach may be to search for biomarkers of the toxic oil syndrome.

Toxicology

8. Toxicity-testing of oils directly related to diagnosed cases has given very limited results. Moreover, a suitable animal model has still not been found. In the light of the negative results obtained from animal studies using authenticated case-related oils, a shift towards toxicity-testing of compounds in oils experimentally refined to simulate the case-related oil would be desirable.

Recommendations

General

1. A workshop should be held for investigators working on either the toxic oil syndrome or the eosinophilia-myalgia syndrome. The aim of this workshop would be to encourage an exchange of information between investigators and to provide an environment in which ideas for collaborative projects might conceivably arise.

Epidemiology

2. To prevent the loss of data, coordination between physicians caring for patients with the toxic oil syndrome and investigators of the disease should be improved. In addition, access to the data needed for statistical analysis of morbidity and mortality would be very helpful.

3. Follow-up studies should include the following:

- systematic collection of clinical data on patients;
- systematic assessment of mortality by cause;
- establishment of a cancer registry in Madrid Province;
- investigation of specific chronic manifestations, such as neuropathy, hepatopathy, sclerodermiform skin changes and pulmonary hypertension;
- collection and analysis of data on congenital malformations, as well as other diseases, in offspring of victims.

In addition, a high priority should be given to the continuation of efforts to establish a properly designed register of the total number of victims.

4. Post-mortem examinations of all victims should be performed and the results entered into a central data bank.

Pathology

5. An inventory of all deaths of victims, regardless of official cause of death, should be established. The inventory should include type and source of autopsy materials available and the interval between exposure to the toxic oil agent and death.

Immunology

6. Three general areas of immunological research should be pursued:
- immunodiagnosis - a search for the immunological characteristics of the syndrome;
 - immunopathogenesis - identification of the components of the immune system involved in tissue injury;
 - immunoeiology - a search for an immunologically active agent that triggers the disease.

Toxicology

7. Priority should be given to the following areas:
- use of nitrogen-labelled aniline to identify and quantify all aniline derivatives in aniline-laden oil put through a simulated refining process;
 - investigation of the toxicity of these aniline derivatives in in vitro systems;
 - identification of non-aniline-related compounds in refined oils;
 - investigation of the toxicity of different oil fractions in laboratory animals;
 - investigation of biologically active compounds or their breakdown products in authenticated case-related oils and non-case-related control oils;
 - development of in vitro and in vivo techniques for bioassays of specific oil components;
 - development of methods by which cells can be exposed to lipids without becoming asphyxiated.