

Toxic oil syndrome, clinical and immunological characteristics: a review

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Summary

In May 1981 a new disease, with epidemic characteristics, appeared in Spain. Initially it was thought that an infectious agent was responsible for the disease, a theory that was later discarded when the disease was found to be associated with the ingestion of adulterated olive oil contaminated with potentially toxic chemicals. More than 20 000 people have been affected, and whilst official reports put the death toll at 250, the true figure may exceed 300. The disease is multi-systemic in presentation, affecting several organs and systems of the body. The disease has a poor prognosis in its chronic stages, which affect approximately 10% of victims, and its ultimate natural history is still to be observed. The pathogenesis of the disease remains to be elucidated, despite considerable efforts already made in this direction.

Introduction

During Easter 1981, a considerable disaster occurred in Spain. A new disease, initially poorly defined, appeared with all the characteristic of an epidemic. In a period of less than 2 weeks there were several deaths and over 230 patients were hospitalized. By August, 2000 people were in hospital and the death toll had risen to more than 100. By the end of February 1982 it was estimated that more than 240 had died and that the total number affected reached 17 000. The immediate explanation given by the health authorities was that this was an infectious epidemic, but this theory was abandoned when the spread of the disease was seen to be untypical of infectious agents and when, furthermore, it was realized that virtually all affected people had consumed olive oil purchased from street vendors. Investigations in this direction revealed that what was supposed to be olive oil was a mixture of grapeseed, rapeseed, cotton and other oils with trace amounts of chemicals such as aniline, parabromoaniline, aminoazobenzene and quinoline, among others. The source of rapeseed oil was from industrial stocks rendered unpalatable by the addition of chemicals to prevent their use as edibles.

Among other treatments, these oils had been subjected to heating to 200°C, to remove the chemicals.

Clinical characteristics

The clinical manifestations in the acute phase were fever, malaise, gastrointestinal upset, pruritus, exanthema and other skin rashes, dyspnoea and radiological findings of pneumonitis and pulmonary transudate. Some cases developed pulmonary distress leading to respiratory failure. There were also neurological manifestations such as headache, sleep-cycle alterations, choreoathetosis and signs of cerebral oedema. After discharge from hospital about 10% of patients were readmitted with fever, anorexia, weight loss, irritability, myalgia, paraesthesia, muscle fibrillations and signs of pulmonary hypertension. Some cases developed polyradiculopathy resembling the Guillain-Barré syndrome. The clinical manifestations of the disease resembled an allergic-toxic syndrome in the acute phase and an autoimmune condition in the chronic phase. Laboratory investigations showed leukocytosis with eosinophilia ranging from 10 to 70%, moderate increase of aminotransferase levels and alkaline phosphatase and, in one fifth of the cases, depressed prothrombin levels (Tabuenca, 1981). Approximately half the cases had raised serum IgE. The histopathological findings were of a vasculitis affecting the capillaries and to a lesser extent the intima, media and adventitia of arteries and veins.

Immunological findings

Serological studies

Several interesting findings have been reported. About one half of the patients have raised serum IgE levels (Tabuenca, 1981). Autoantibodies were tested by immunofluorescence: one group of patients exhibited increased gastric parietal cell antibodies (16%) whilst the prevalence of non-organ-specific antibodies (antinuclear antibodies, anti smooth muscle, etc.), were within normal limits. A second group of patients, mainly from people with chronic sequelae of the disease, including neurological symptoms, showed a slight increase in non-organ-specific antibodies, including striated muscle antibodies, at low titre (F. Bottazzo, personal communication). We confirmed elevated IgE levels in about 45% of patients and noted that these levels decreased as the disease progressed (Brostoff *et al.*, 1982).

In an attempt to define the responsible antigen we developed a solid-phase assay to detect IgE-specific antibodies for the chemicals alleged to have been added to the oil (Brostoff *et al.*, 1982). The chemicals were bound in different ways to the solid phase matrices, and a radiolabelled anti IgE was used to detect the binding of specific antibodies to these solid-phase preparations. We further tested for IgG and IgM antibody by sheep red blood cell haemagglutination, using human serum albumin conjugates of various contaminating chemicals. In none of these cases did either radioimmunoassay or haemagglutinin detect any specific antibody to the chemicals said to be contaminating the oil.

Cellular studies

Lahoz *et al.* (1981), have found a decrease in E-rosetting T cells, OKT-3 and OKT-8 positive lymphocytes, but normal OKT-4 positive cell levels, suggesting an alteration in the regulation of the immune response, perhaps allowing the production of

autoantibodies, and high IgE levels. There is evidence that HLA-DR factors influence susceptibility to the chronic stage of the disease, in that DR3, DR4, and DR3/4 are significantly represented in chronically affected females. Lymphocytotoxic antibodies were also reported in both stages of the disease (Vicario *et al.*, 1982).

Discussion

Hypotheses as to causation

When the initial infectious agent theory was discarded, research was directed toward the chemical contaminants of the oil (aniline, p-bromoaniline, aminoazobenzene, etc.). Previous to this, toxic manifestations of aniline were confined to industrially exposed workers who exhibited cyanosis and methaemoglobinaemia. Thus, aniline seemed an unlikely candidate as the responsible agent. New compounds of aniline derivatives which had formed spontaneously in the mixture, such as anilides, were found in the oil. These compounds, being lipophilic, can enter the plasma membrane and penetrate the cell. *In vitro* experimental evidence exists supporting the possibility that these fatty-acid anilides could cause cell-membrane perturbations, with the possibility that they exert a toxic effect this way (Murphy & Vodyanoy, 1982). Another possible theory was that during the metabolism of these compounds free radicals and peroxide were produced with the capability of damaging the plasma membrane (Tabuenca, 1981). A less-favoured hypothesis was that the oil, being low quality and unrefined, could be contaminated with several moulds and that mycotoxins could be responsible for the disease (Schoental, 1982). So far there is no definite proof of any of these theories, neither is there a useful experimental model of the disease in animals (Tena, 1982). It should also be borne in mind that these compounds are similar to known carcinogens and that further long-term effects, i.e. neoplastic diseases, may yet manifest themselves (Robert & Warwick 1963, Scribner, Miller & Miller, 1965).

Therapeutic considerations

Several therapeutic approaches have been used. Vitamin E was used in the hope that its action as a 'scavenger' of free radicals would be beneficial, but with no apparent success. The use of the chelating agent penicillamine was likewise unsuccessful, as was the use of polyvinylpyrrolidone. Corticosteroids were said to have beneficial effects on fever, skin manifestations and pneumonitis, although controlled studies are lacking.

In conclusion, the aetiology and pathogenic processes of the disease are still enigmatic and challenged the resources of more than twenty academic medical centres who come to no firm conclusion other than that the syndrome is a manifestation of a new disease process.

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