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Plenary Lectures and Abstracts

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PLENARY LECTURES

REYE AND REYE-LIKE SYNDROMES: EPIDEMIOLOGY AETIOPATHOGENESIS AND DIAGNOSTIC PROBLEMS IN THE BRITISH ISLES

Susan M. Hall

Public Health Laboratory Service, Communicable Disease Surveillance Centre, (CDSC), LONDON

Introduction

Reye's Syndrome (RS) is a rare, serious childhood encephalopathy preceded by a viral prodrome and associated with hepatic dysfunction characterised by elevated serum transaminases, plasma ammonia and diffuse, microvesicular fatty infiltration of the liver. Its aetiology and pathophysiology are poorly understood but causation is probably multifactorial. In the United States (US) most cases are associated with influenza and chickenpox although series from other countries have implicated a wide variety of viruses. Various toxic agents have also been implicated, including aflatoxins, margosa oil, insecticides and their emulsifiers. An association with aspirin was documented in five case control studies conducted in the US. As a result, warning labelling on all aspirin containing products and a public education campaign was instituted in 1985 in that country. In addition to the exogenous factors, an innate susceptibity is probable. This has, however, not yet been delineated, although it is likely to involve hepatic and possibly other mitochondria because there is specific morphological and biochemical evidence of derangement of these organelles in RS.

In recent years there has been increasing evidence that certain inborn errors of metabolism, notably urea cycle defects and disorders of fatty acid oxidation may present with an identical clinical, biochemical and histological (but not ultrastructural) syndrome. Limited diagnostic awareness and laboratory expertise may lead to these patients being misclassified as having RS thereby confusing the epidemiological findings.

The British Reyes Syndrome Surveillance Scheme (BRSSS)

a. Aims and Methods

National surveillance of RS in the British Isles began in August 1981 with the aims of documenting the descriptive epidemiology (and comparing this with the US findings), monitoring long term trends and providing a database for more detailed clinical, pathological and epidemiological studies. It is a joint venture between the British Paediatric Association and CDSC. Until June 1986 case ascertainment was passive, depending on voluntary clinical reports from consultant paediatricians. Active reporting via a monthly card sent to all paediatricians began in July 1986 with the inception of the British Paediatric Surveillance Unit (BPSU). The case definition used is the same as that used for surveillance in the US. Detailed clinical and epidemiological information is requested on each reported case.

An epidemiological case-only risk factor study to develop aetiological hypotheses was conducted 1984-5. A comparison group was recruited in the second year in order to determine more specifically the role of aspirin in RS.

b. Findings

Annual numbers of cases reported in the five years 1.8.81 - 31.7.86 were: 40, 57, 81, 53, 38, giving an annual incidence per 100,000 children under 16 ranging from 0.6 to 0.3. This is comparable with US national surveillance results but other epidemiological features were different - notably a younger median age, 14-16 months (cf 6-8 years in US); a lower proportion with varicella prodrome but a higher proportion with no clear prodrome; a wide variety of viruses identified; no clear winter peak; a lower incidence in blacks. There was a significant excess incidence in N. Ireland. Each year a number of cases were reported who initially satisfied the case criteria but who later had their diagnoses revised (not included in above figures). The proportion of reports formed by these patients increased from 16% in 1981/2 to 44% in 1986/7. The most frequent revision was to an inborn error of metabolism.

The results of the risk factor study showed that a significant excess of cases (59% vs 26% in the comparison group) had been given aspirin. When cases were allotted a score based on all the clinical and pathological features of RS described in the US, a highly significant correlation was found - nearly all patients with the highest scores had taken aspirin.

In June 1986 the Committee on Safety of Medicines (CSM) issued a public and professional warning about aspirin use in children with fevers. Paediatric aspirin preparations were voluntarily withdrawn and warning labelling instituted. Since then, in spite of the introduction of a more sensitive surveillance method (the BPSU, which caused a marked increase in ascertainment of Kawasaki Disease and Haemolytic Uraemic Syndrome) the number of cases 1.8.86 - 31.7.87 was the lowest ever reported: 27; the incidence in N. Ireland in particular has declined dramatically.

Comment

There are currently only 2 long term national surveillance schemes for RS: those in the US and in the British Isles; other countries have however reported limited series of cases. A comparison of epidemiological features shows that RS in the US appears to be different from that in Britain which in its turn is similar to that described elsewhere. The principle differences are the younger age and the weaker association with influenza and chickenpox. It is suggested that 'North American - type' RS is a distinct entity with a strong association with aspirin (this type has now declined in incidence in the US and a higher proportion of 'British-type' RS is currently seen). In contrast, because of the non-specificity of the case definition which is, however, both practical and senstive, 'British-type' RS may include a high proportion of patients with unrecognised inborn errors of metabolism. The role of aspirin in precipitating encephalopathic episodes in those disorders has not been assessed. It is, however, crucial that diagnostic awareness and expertise are increased because of the implications for management and prevention.