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AMYLOIDOSIS IN RHEUMATOID ARTHRITIS TREATED WITH HORMONES

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Experimental evidence suggests that treatment with cortisone or ACTH increases the rate of accumulation of tissue amyloid. Thus Teilum (1952) has shown that mice previously treated with casein in doses insufficient to cause amyloidosis accumulate amyloid quickly in the spleen after a small number of injections of cortisone. Latvalahti (1953) has confirmed this observation and has shown that mice given either cortisone or ACTH develop amyloidosis much more frequently when given caseinate than mice given caseinate alone. Similar studies have been made by Peräsalo (1954).

Widespread amyloidosis of secondary distribution is now recognized with considerable frequency in rheumatoid arthritis (Missen and Taylor, 1956; Cruickshank, 1957). For some time it has seemed possible that the incidence of amyloidosis in this disease may be rising as the result of the widespread therapeutic use of cortisone and other steroids and of ACTH. The alternative possibility, that an apparent increase in the incidence of amyloidosis may have resulted from contemporary interest in the pathological characteristics of rheumatoid arthritis, has received less attention.

More than 10 years have elapsed since the introduction of cortisone therapy. It appears reasonable to examine the available records of cases of rheumatoid arthritis which have come to necropsy in this centre in an attempt to answer the question posed by the provocative experimental evidence.

Material and Methods

The records of 54 patients with rheumatoid arthritis who died during the period 1954-1960 were examined. 35 of these necropsies were conducted personally, and in the remaining instances extensive histological material was available. Sections of all relevant organs likely to contain amyloid were stained with methyl violet and with Congo red. Those cases in which amyloid of classical tinctorial characteristics was readily and widely recognized were accepted as positive. Doubtful cases were regarded as negative.

An identical procedure was adopted with the 54 most recent cases of rheumatoid arthritis examined in this centre in the pre-cortisone era. The cases covered the period 1935-1950. None had been conducted personally and in most the material available for histology was more limited than in the first group. Again, only those cases with unequivocal evidence of widespread amyloid deposition were accepted as positive.

Results

(A) *Pre-cortisone Era* (1935-1950).—Five cases (9·3 per cent.) were found to have generalized amyloidosis of secondary distribution.

(B) *Cortisone Era* (1954-1960).—Eight cases (14·8 per cent.) were found to have generalized amyloidosis of secondary distribution, and one of them was recorded as having been treated with cortisone.

Among the 54 cases of this second group, four had been treated rigorously with cortisone, two with ACTH, one with prednisone, and one with prednisolone. Among these eight cases treated with hormones there was therefore only one (12·5 per cent.) with amyloidosis.

Discussion

A direct comparison of the two groups of cases of rheumatoid arthritis is impossible, since many factors other than therapy have changed during the past 25 years. It is likely, for example, that diets are no longer precisely similar. With this proviso, there is no reason to believe from the present results that the incidence of generalized amyloidosis has increased. It is salutary to reflect that amyloidosis has been a common feature of rheumatoid arthritis for many years.

Further evidence is provided by the more detailed analysis of the 1954-1960 group. Only one of

eight cases with amyloidosis had received hormone therapy and only one of eight cases given hormones had amyloidosis. It seems likely that the amounts of these drugs used clinically are less effective than those found to precipitate amyloid formation in the experimental animal. The deposition of amyloid experimentally is extremely rapid by comparison with the rate of formation in the patient with rheumatoid arthritis.

There is therefore no reason to believe that the therapeutic use of steroids and ACTH in rheumatoid arthritis has increased the already high incidence of secondary amyloidosis.

Summary

(1) The necropsy records of 108 cases of rheumatoid arthritis were studied and the incidence of generalized secondary amyloidosis determined. In 54 patients who died before the introduction of cortisone therapy (1950) there were five instances (9·3 per cent.) of amyloidosis. In 54 patients who died between 1954 and 1960 there were eight instances of amyloidosis (14·8 per cent.).

(2) Of the eight cases of generalized amyloidosis who have come to necropsy since the introduction of cortisone, only one had received steroid therapy. By contrast, five of the 54 recent cases of rheumatoid arthritis were known to have been treated with steroids but were not found to have amyloidosis.

(3) In spite of the experimental evidence, the available information does not support the suggestion of an increase in secondary amyloidosis in rheumatoid arthritis as the result of the use of hormone therapy.

Some of the present series of cases were studied during the tenure (1954-1956) of a research fellowship at the Rheumatism Research Unit, Northern General Hospital, Edinburgh, which was in receipt of grants from the Medical Research Council, the Nuffield Foundation and Boots Pure Drug Company. More recently, the analysis of cases has been aided particularly by Dr. Neil Maclean of the Western General Hospital, Edinburgh.

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Amyloïdose dans l'arthrite rhumatismale traitée par des hormones

RÉSUMÉ

(1) On étudia les dossiers d'autopsie de 108 cas d'arthrite rhumatismale et on nota la fréquence d'amyloïdose généralisée secondaire. Parmi 54 malades morts avant l'introduction de la thérapie par la cortisone (1950), il y eut cinq cas (9,3%) d'amyloïdose. Parmi 54 malades morts entre 1954 et 1960 il en eut huit (14,8%).

(2) Sur huit cas d'amyloïdose généralisée parvenus à l'autopsie depuis l'introduction de la cortisone, on n'en connaît qu'un seul qui ait reçu le traitement stéroïde. Par contre, parmi les 54 cas récents d'arthrite rhumatismale, il y en eut cinq traités par des stéroïdes qui à l'autopsie ne révélèrent pas d'amyloïdose.

(3) Malgré les données expérimentales, les renseignements actuels ne supportent pas l'opinion que l'augmentation de l'amyloïdose secondaire dans l'arthrite rhumatismale soit due à la thérapie hormonale.

Amiloidosis en la artritis reumatoide tratada con hormonas

SUMARIO

(1) Se estudiaron las fichas de necropsia de 108 casos de artritis reumatoide y se notó la frecuencia de la amiloidosis generalizada secundaria. Entre 54 enfermos que murieron antes de la introducción de la terapia con la cortisona (1950) hubo cinco (9,3%) casos de amiloidosis. Entre 54 enfermos que murieron entre el 1954 y el 1960 hubo ocho (14,8%) casos.

(2) Entre ocho casos de amiloidosis generalizada llegados a necropsia después de la introducción de la cortisona, se conoce un solo que habia recibido el tratamiento steroide. En cambio, entre los 54 casos recientes de artritis reumatoide, hubo cinco que habían sido tratados con steroides sin revelar una amiloidosis a la necropsia.

(3) A pesar de los datos experimentales, los conocimientos actuales no prestan apoyo a la opinion de que el aumento de la amiloidosis secundaria en la artritis reumatoide sea debido a la terapia hormonal.