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NOTES OF MEETING OF SNBTS COAGULATION FACTOR (NEOANTIGEN STUDY GROUP MEETING) 9TH MAY, 1985

Attendance: JDC, DSP, JD, PLY, FEB, R MacIntosh, Dr Graham Bird (Newcastle), CP

1. Dr Bird discussed the immunological considerations regarding the development of neoantigens on heat treatment (outline attached) and also discussed the data from the review by Benacerraf (attached).

2. Ron MacIntosh then outlined the heat treatment steps that were being considered for Factor VIII, all of which involved dry heat. These consisted of:
   68C x 10h (current method)
   68C x 24h (for HTLVIII inactivation)
   80C x 3 days (hepatitis B type inactivation)
   The form of heating that was preferred was dry heat rather than wet heat because of the problem of developing appropriate stabilizers for wet heat.

3. Dr Bird felt there were two separate problems: the development of neoantigens to Factor VIII, particularly in patients who are totally deficient in Factor VIII and the development of neoantigens to contaminants of Factor VIII concentrates (fibrinogen, fibronectin, IgG and complement in order of concentration) for which tolerance was already present. A particular point made was that fibrinogen and immunoglobulins were possibly more polymorphic and likely to aggregate and discussion ensued / concluding that the 10% of patients with inhibitors might be a prime group for study. Dr Bird had had discussions with Dr Dresser who felt that there was serious potential risks in the long term of the development of autoantibodies to neoantigens and Dr Bird emphasised that the two steps which were involved in heat treating Factor VIII i.e. aggregation and intravenous administration might result in increasing immunogenicity. However, soluble antigen was usually tolerogenic and Dr Bird emphasised that the studies on neoantigens undertaken in the 1960s (see review by Benacerraf) involved the use of adjuvant.

4. Some discussion ensued about the possibility that chronic administration of large amounts of proteins might block the RE system with an increase in the infection rate.

5. JD presented some data obtained about two years ago in an attempt to look at the effect of wet heat on various proteins that sensitive immunoassays existed for. Of the proteins studied (PF4, thrombospondin, Factor VIII and Fibrinogen) only fibrinogen showed the suggestion of a change in antigen structure on heating .

6. Ron MacIntosh described In Confidence the preliminary findings when IgG molecules were treated at 80C x 3 days, the only functional abnormality was complement binding at the CH_2 domain.

7. Much discussion ensued about possible ways of experimentally approaching this problem. It was generally agreed that animal experiments were difficult to do and might not be relevant. It was also agreed that differentiation was necessary between the immediate adverse reactions to heat treated Factor VIII infusions and the long term effects.

8. It was agreed that only HTLVIII sero negative patients should be studied since immunological abnormalities might arise in the latter group of patients and there might be problems in handling the samples even if they were available.

9. The following suggestions were made about possible ways of evaluating the development of new antigens and other related immunological phenomena:

   a) <u>Clinical Studies</u>:

      i) Evaluation of RE function e.g. by the infusion of heat treated erythrocytes or antibody coated erythrocytes (action: JDC, to contact a group in Glasgow with a possible interest in this technique).

      ii) Prospective study of infections and other clinical phenomena e.g. antibiotic usage, a note of all illnesses, skin rashes etc. PLY suggested that this might be something that the research nurse looking after the haemophiliac patients might be able to review on a monthly basis with the haemophiliacs in a manner similar to the hypogammaglobulinaemia study (action: JDC to raise with haemophilia directors).

b) Immunological assays: The following to be considered:

i) Total IgG
ii) Anti fibrinogen
iii) Rheumatoid factor (Dr Bird says they may increase)
iv) Factor VIII inhibitors
v) Bacterial antibodies e.g. anti E coli
vi) CRP
vii) Fibronectin (opsonic depletion)
viii) Immune complexes
ix) Chronic changes in complement levels (for retrospective study only: requires frozen samples stored sequentially)
x) Antibodies to the Factor VIII product by ELISA

c) CP and FEB mentioned that there were a number of samples from haemophiliac patients already stored in Edinburgh BTS which had been collected as part of the evaluation of the new heated Factor VIII. JDC requested that CP/FEB make a list of what samples they had.

d) JDC requested that all future infusions of Factor VIII should be accompanied by measurements of heparin levels to see if any adverse reactions were occurring immediately after infusion.

e) It was agreed that PLY should contact Dr Dresser and Professor Humphrey to find out if they had further suggestions.

10. JDC said that the problem of assays would be remitted to a small working group (DSP, JD et al) and that he would be approaching the Haemophilia Directors about the possibility of initiating a long term study in this area.

11. Ron MacIntosh was asked to provide a specification if possible of heated treated Factor VIII and also to provide 10 paired heated and unheated batches of Factor VIII for assay by DSP/JD/CP (DSP to act as co-ordinator).

NOTES BY P L YAP
14 May 1985