PART VII

BIOCOMPATIBILITY

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HYPERSENSITIVITY REACTIONS DURING HAEMODIALYSIS IN FRANCE

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Summary

A retrospective survey was conducted in 112 French haemodialysis units from 1977 to 1984; it revealed 111 observations of hypersensitivity reactions to haemodialysis equipment. The important predisposing factors are: a history of atopy and hypereosinophilia (27%), the nature of the sterilizing agent (ethylene oxide); the nature (cuprophan involved in 87%) and form (fibre in 76%) of the membrane and the rinsing procedure.

Introduction

Acute anaphylactoid reactions in haemodialysis have been described since 1980 [1,2]. They occur as early as the first few minutes of the dialysis and produce clinical effects suggestive of histamine release (hypotension, bronchospasm, chest pains, urticaria, sneezing, wheezing, coughing, nausea, vomiting and a feeling of imminent death). As they are relatively rare, each dialysis team obtains only a very limited experience. The first large series was recorded in 1982 [3]; 23 cases, two being fatal. The term 'First use syndrome' has been suggested.

Various mechanisms have been proposed: activation of complement [4,5], IgE mediated anaphylaxis, the action of toxic or allergenic components of the dialyser membrane, blood lines or sterilization products, and contamination of the dialysate. Some have lumped together a number of adverse reactions connected with bio-incompatibility under the term 'symptomatic hypotension'.

The occurrence of a fatal reaction in one of our patients at the very start of a dialysis session prompted us, after a full review of the literature, to undertake an epidemiological survey in France, comparable to the one made by the Food and Drug Administration in 1983 [6].

Methods

One hundred and twelve haemodialysis centres, representing 55 per cent of all French units, took part in this survey, providing details of 111 patients who had

suffered one or more reactions in 52 units. No reactions at all had occurred in 60 units. This retrospective survey was performed in 1983 and essentially concerned 1982 and 1983, with, however, a few previous observations (1977 to 1981). As it was retrospective, we have been unable to draw any statistical conclusions.

We used the Hamilton classification [7] to assemble the observations in three groups, depending on their severity.

Results

Distribution of hypersensitivity reactions in time

Ninety-one observations could be accurately dated, while 20 more dated from 1982, 1983 and 1984, but without any further details. Their distribution is shown in Table I. It will be noted that the incidence of reactions is much greater in 1982 and 1983 (65% of the accurately dated incidents).

TABLE I. Number of hypersensitivity reactions from 1977 to 1984

Date	1977	1978	1979	1980	1981	1982	1983	1984	Non-dated	Total
Number	1	6	1	2	6	16	43	16	20	111
11 reactions in 52 units				31 mild reactions in 21 units 54 moderate reactions in 31 units 26 severe reactions in 21 units (including 4 deaths)						

Age, sex, duration of haemodialysis

Hypersensitivity reactions occurred at any age (7 to 78) with no difference in distribution between the sexes. Sixty-five per cent of the severe reactions occurred in patients who had been undergoing haemodialysis for less than a year, 40 per cent between two and five years, 25 per cent between six and 10 years, and 10 per cent after 10 years of treatment. The incident occurred during the first haemodialysis session in three patients.

Clinical features

Eosinophilia (over 350/mm^3) and atopy existed in 27 per cent of the patients suffering reactions, with a preponderance in the severe reactions group (48% of these are hyper-eosinophilic and 32% atopic). Eighty-seven per cent of the reactions begin before the 15th minute. All the severe reactions took place before the 10th minute, whereas observations of milder reactions were spread out over the first hour of dialysis.

The clinical symptomatology was very varied, 30 symptoms were observed and the intensity of the reactions noted in the three groups (cf Table II), e.g.

TABLE II. Signs and symptoms of hypersensitivity reactions

	Stage I	Stage II	Stage III
Mild systemic reactions	Pruritis, urticaria, erythema Eczema, warm sensation, sick feeling Nasal congestion and peri-orbital swelling Lacrimation Sneezing Oedema of the arm of fistula Tightness of the chest Abdominal pains	MINOR SIGNS +	MODERATE SIGN
Moderate systemic reactions		Oedema of airways Mild bronchospasm Dyspnoea, cough wheezing Generalized urticaria Nausea, vomiting, diarrhoea	+
Severe systemic reactions			Feeling of impending death Intense bronchospasm and laryngeal oedema leading to cyanosis Intense abdominal cramp Cardiovascular collapse and respiratory distress leading to hypotension and hypovolaemia shock and death

acute respiratory distress could be preceded by a few moments of minor or medium symptoms.

The evolution was simple in 38 patients (type I and II), but necessitated treatment in 83 (antihistamines and/or low doses of corticoids). In 35 cases, the clinical intensity (essentially type III) made it necessary to terminate the dialysis and institute resuscitation, despite which four patients died.

Reactions recurred 69 times (62%) and in two-thirds of the cases, when the same membrane was used; in 59 cases changing the membrane helped to reduce or prevent reactions (in 29 cases a synthetic membrane was then used). Two patients suffered episodes with all existing haemodialysers necessitating transfer to continuous ambulatory dialysis.

Biology

The lack of current knowledge of the pathophysiological mechanisms and the difficulties in measuring their biological expression (histamine, leukotrienes, C_3a, C_5a), of which only some specialist laboratories were capable, and the sampling requirements (centrifuging, immediate deep-freezing) explain the relative dearth of biological data. We were nevertheless able to obtain deep-frozen sera from 22 patients exhibiting reactions compared with 45 reference patients who did not, for research into the specific IgE of ethylene oxide (dosed by Phadezym RAST test) in Enka's laboratory in Obernburg (FRG). Four patients of the 22 with reactions of types II and III had a specific IgE rate greater than 0.35PRU/ml (as against 3/45 non-clinically reactive in the control sample).

Eosinophilia $<350/mm^3$ was found in 19 of 55 patients.

Equipment (Table III)

In 87 per cent of cases, the haemodialyser used on the occasion of the first reaction had a cuprophan membrane, in fibre form in 76 per cent of cases. No reaction occurred with a reused dialyser. Whilst the question was not asked, it was spontaneously stated that the accident occurred on 10 occasions on the day when the dialyser was being changed for the patient (first use of a dialyser with a different brand membrane). Seventy-five per cent of the reactions occurred when the equipment had been rinsed with less than one litre.

TABLE III. Haemodialysers: used brands

	Number of reactions Amount per cent	Stages of the reactions and number of reactions		
		minor	moderate	severe
Cuprophan				
Fibres	84=76%	26	41	17
Flat sheets	10= 9%	1	5	4
Coils	2= 2%	0	1	1
Polyacrylonitrile				
AN 69	8= 7%	1	4	3
Others PAN	2= 2%	1	2	1
Haemofilters	4= 4%	0	1	0
Cellulose acetate	1= 1%	0	1	0

Discussion

The frequency of the incidents in time, greater in 1982 and 1983, parallels observations in the USA (362 cases in these two years) and data in the literature

(85 reactions, most dating from the 'eighties). During the same period, the use of hollow-cuprophan haemodialysers became more widespread; in 23 centres which informed us of the quantity of hollow fibre dialysers used, there were three reactions in 1978 (with 47,824 dialysers) and 43 in 1983 (with 160,537 dialysers). Therefore there seems to be a correlation between the use of cuprophan fibre dialysers and the increase in the frequency of bio-incompatibility reactions, as suggested by most authors.

The occurrence of hypersensitivity reactions at any age and for however long haemodialysis had been undertaken (from the first session to the thirteenth year) means that very careful attention must be paid to any new symptom appearing on connection. The high frequency of hypereosinophilia and atopy, in particular in the severe reaction group, means that eosinophilia must be regarded as a hypersensitivity reaction risk factor. Eosinophilia must be looked for in all patients subjected to haemodialysis.

The clinical features may be very serious and we feel that any type II or III reaction must be treated in the following manner: the dialysis must be stopped immediately, the blood must not be returned to the patient; adrenaline must be used, corticosteroids must be administered and a synthetic membrane must be used for subsequent dialyses. The toxicity of ethylene oxide by reactions linked to the presence of specific IgE has been proven in a small number of cases. It could be latent, since significant rates are found in clinically asymptomatic patients, whereas some of them could be carriers of blocking IgG.

Variability in equipment shows up complex factors: intolerance reactions to a membrane cease when a different one is used; the use of a proper rinsing procedure (2 litres or more) eliminates certain reactions, perhaps by removing certain materials found by high pressure liquid chromatography in trace amounts [8]; the contamination of the bath by organisms producing endotoxins could have brought about severe reactions, with some highly permeable membranes, which disappear with the elimination of microbial growth.

In cases of the first use syndrome the reaction seems to occur preferentially in atopia; the existence of specific IgE could indicate a mechanism helped by IgE, with ethylene oxide having been shown as a hapten in some observations, but other haptens or sterilizing allergens or haemodialyser manufacturing products for which there are as yet no detection tests available could also be important. It would therefore seem necessary to draw up an allergological balance sheet for the constituents and sterilizers of the equipment (haemodialysers, lines, etc).

The reactions of certain patients seem to occur specifically with certain membranes, thus posing the problem of membrane-dependent reactions, as proposed by Kessler [9]. The intensity of the fall in the neutrophils and in complement activation, varies with the membrane used, and is greater with cuprophan than with synthetic membranes, probably reflecting the latter's better bio-compatibility. Theories of complement hyperactivation and/or of the prevalence of the antigen MO-1 in certain patients have recently been put forward, thus raising the problem of individual susceptibility.

The biological effects of the production of Interleukin I by the macrophages and monocytes activated by the haemodialysis equipment account for a large

number of adverse reactions grouped under the term 'symptomatic hypotension' [10] and long-term bio-incompatibility effects.

All haemodialysis patients are at present exposed to the risk of hypersensitivity reactions but with a higher frequency when there is an allergic history and equipment which is biologically incompatible with the patient by its nature or use. The rarity of incidents and our poor present knowledge of their mechanisms necessitate a deep investigation, which can be performed by grouping observations in the form of a prospective survey now being made in France, so that incidents may be prevented by the abandonment of potentially harmful equipment through the joint vigilance of medical teams and manufacturers.

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