Immunoglobulin levels in infantile pneumocystosis

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SYNOPSIS Two hundred and twelve determinations of IgA, IgG, and IgM were performed in 50 infants during an epidemic of interstitial plasma cell pneumonia. Criteria for diagnosis are discussed. The immunoglobulin levels in pneumocystic, non-pneumocystic, and normal American infants are compared. An analysis of the findings in individual cases reveals a time-related immunoglobulin response, which helps to elucidate the pathogenicity of the disease.

Pneumocystis carinii is an unclassified saprophyte of the tracheobronchial tree of many animal species (Delanoë and Delanoë, 1912; Weller, 1955; Jirovec, 1960) and is also found as a commensal in the human trachea (Esterly and Warner, 1965; Hamlin, 1968). Intraalveolar clusters of *Pneumocystis carinii* contain varying numbers of encysted forms with eight merozoites within a capsule, which is highly antigenic (Brzosko, Nowosławski, and Madaliński, 1964), and consists of chitosamin, lipoproteins, and mucopolysaccharides (Bruns, 1955). Human infection with *Pneumocystis carinii* is always associated with some form of immune deficiency.

The human host response varies greatly with the underlying immune defect. Three basic forms can be distinguished:

(1) Hypoergic, hypimmune pneumocystosis which occurs in drug or radiation-induced hypimmune states following transplantation (Rifkind, Starzl, Marchioro, Waddell, Rowlands, and Hill, 1964), after prolonged cortisone therapy (Kossel, 1962), or in cases of inherited immune deficiency (Marshall, Weston, and Bodian, 1964; Robbins, Miller, Areal, and Pearson, 1965). This form of pneumocystosis is characterized by the absence of interstitial plasma cell infiltration of the alveolar septa, immune response to the organism, and consequently negative serology. Experimental pneumocystosis is a complete model of hypoergic, hypimmune pneumocystosis (Weller, 1955; Linhartová, 1958; Sheldon, 1959).

2 Massive, panlobar interstitial plasma cell pneumonia of infants, which was first observed in nursery and orphanage epidemics in Europe after World War II, occurs only in the 2-6-month age

group and is often fatal due to alveolar capillary block caused by the massive interstitial plasma cell infiltrate in the alveolar septa (Dvořák and Jirovec, 1953; Jirovec and Vanek, 1954; Gajdusek, 1957; Koop, 1964).

3 Focal subclinical interstitial plasma cell pneumonia of infants, which is an abortive form of interstitial plasma cell pneumonia, occurs under the same conditions but is recognized only as a chance finding at necropsy or due to the positive complement-fixation reaction after the disease is terminated (Hamperl, 1957; Woodward and Sheldon, 1961).

An epidemic in a Shiraz orphanage with a high mortality rate (Table I) was studied between 1962 and 1968 (Post, Dutz, and Nasarian, 1964; Thomas, Dutz, and Khodadad, 1966; Dutz, 1970).

Total necropsies	..	..	..	..	..	..	300
Orphanage necropsies	..	..	..	..	..	..	186
<i>Cause of Death of Orphanage Infants</i>							
Pneumocystosis	..	..	..	..	..	..	68
Other infections	..	..	..	..	..	..	55
Malformations, congenital	..	..	..	..	..	..	39
Aspiration	..	..	..	..	..	..	24
Total	..	..	..	..	..	..	186

Table I *Infants necropsied at Pahlavi University, Shiraz, 1961-1967*

All the children suffered from severe diarrhoea, marasmus, and many intercurrent infections. The bowel mucosa showed severe atrophy and tropical sprue (Creamer, Dutz, and Post, 1970). To elucidate the conditions leading to interstitial plasma cell and focal subclinical pneumonia the qualitative and quantitative levels of IgA, IgM, and IgG were studied.

Materials and Methods

Sixty-five infants admitted to the orphanage shortly after birth in the period from January 1966 to January 1968 were studied. Complete clinical charting was introduced. Special attention was paid to respiratory signs and symptoms. The following tests were performed once monthly, more often if clinically indicated: chest radiographs; complement-fixation test with the Barta (Bárta, Dvořáček, and Kadlec, 1955) and later the Vivell (Vivell, 1955) method; tracheal aspiration with direct laryngoscopy and bronchial catheterization, sublimate fixation of smears and Giemsa staining. The microscopic examination and interpretation of the aspirates was performed by one pathologist only. Serum was obtained from each infant by intravenous puncture once a month for immunoglobulin determination, more frequently if indicated by symptoms as for instance during a respiratory crisis with cyanosis. Serum protein levels were determined by the microbiuret reaction, simultaneous analysis by paper electrophoresis, and cellulose-acetate microelectrophoresis with the Beckman Analytrol system. Immuno-electrophoresis in agar gel plates against antihuman IgA, IgM, and IgG was performed separately. Quantitative levels of IgA, IgM, and IgG were determined with Highland immunoplates and compared with the Highland standard.

Additionally immunofluorescent studies were performed on several selected lungs to determine the levels of IgA and IgM in the alveoli. The lungs of two infants with diffuse interstitial plasma cell pneumonia and marked *Pneumocystis carinii* infestation were removed at necropsy within two hours after death and immediately frozen in a deep freeze chest below minus 40 degrees Centigrade. They were kept frozen for four and six months respectively. The control lungs were stored and frozen under identical conditions in the same freezer. The following controls were used: the lung of a 3-month-old infant without pulmonary disease, stored for three months; the lung of a 6-month-old infant without pulmonary disease stored for five months; the lung of an infant aged 3 months dying of bronchopneumonia, stored for six months; the lung of a 6-month-old infant with thymic alymphoplasia of Bruton type stored for one month; and the lung of a normal adult stored for five months. Eight cryostat sections were prepared from different areas of each lung.

Rabbit antihuman IgA and IgM (Burroughs Wellcome) was diluted in isotonic phosphate buffer 1:20 and 1:40 immediately before use. Horse anti-rabbit immunoglobulin conjugated with fluorescein-isothiocyanate was diluted 1:5 in isotonic phosphate buffer. The frozen sections were washed by dipping

into isotonic phosphate buffer three times, air dried in a 37°C incubator, covered with acetone for 10 minutes, dried again as before and then covered with the rabbit antihuman IgA and IgM for 20 hours in a moist chamber at 4°C. The slides were then thoroughly washed with isotonic phosphate buffer, dried and exposed to fluorescent horse antirabbit immunoglobulin and incubated in a moist chamber at room temperature for one hour. The sections were then thoroughly rinsed again in isotonic phosphate buffer, mounted in pure glycerin diluted with buffered saline, and examined under the fluorescent phase contrast microscope (Coons and Kaplan, 1950; Coons, Leduc, and Kaplan, 1961).

The results of the immunoglobulin fluorescent staining of two lungs with interstitial plasma cell pneumonia and several control lungs stored under the same conditions show a marked predominance of IgM in the alveolar walls and coating the alveoli with complete absence of IgA (Table II).

	Alveolar Fluorescence	
	IgA	IgM
Pneumocystic lung	-	+++
Infant 3 months	+	-
Infant 6 months	+	-
Infant with bronchopneumonia	+	+
Infant with Bruton's disease	-	+
Normal adult lung	++	-

Table II Presence of alveolar fluorescence

Discussion

Several series of quantitative immunoglobulin determinations in nursery epidemics of pneumocytosis are reported (Koltay and Illyés, 1966; Pozzuoli and Corda, 1966; Pozzuoli, Parma, and Costanzi, 1966), in which no specific time relation to the radiological lesion was established and stringent diagnostic criteria beyond those of clinical and radiological suspicion were not applied. The results conform essentially to our unsorted data, not distinguishing between interstitial and focal plasma cell pneumonia.

The clinical picture of severe interstitial plasma cell pneumonia is characterized by a rapidly developing cyanosis and tachypnoea with air hunger, frequently leading to death within 24 hours after onset. The pathological substrate is a massive interstitial plasma cell infiltration of the lung. Kouvalainen, Hjelt, and Wasz-Höckert (1964) described a case with marked elevation of beta 2 M (IgM) globulin during a lethal respiratory crisis. Studies with fluorescent IgM showed specific coating

Group	No. of Clinical Cases	Symptoms				Laboratory			Deaths	Necropsy	Diagnosis	Result
		Cough	Retraction	Tachypnoea	Cyanosis	Radiograph	Aspirate	Serology				
I	6	6	6	6	6	+	+		6		Diffuse interstitial plasma cell pneumonia	+
II	14	14	14	14	2	+	+	+	1		Late death, unspecific infiltrate	+
III	8	8	6	6	2	+	-	+	1		Late death, unspecific infiltrate	+
IV	5	5	3	3	0	-	-	+	1		Late death, unspecific infiltrate	+
V	7	7	7	7	5	+	+	?	0			Probable
VI	6	6	6	6	2	+	+	-	0			-
VII	19	19	16	17	2	+	-	-	0			-
Total	65	65	58	59	19				9			33 confirmed diagnoses

Table III Sixty-five cases of clinically suspected pneumocystosis January 1966 to July 1968

of the pneumocystis capsules (Brzosko, Madaliński, and Nowosiłowski, 1967).

Focal pneumocystosis cannot be differentiated from other pulmonary infiltrations on clinical or radiological grounds. Only a positive serological test, which occurs three to six weeks after the onset of pneumocystosis, is of diagnostic value (Table III). Necropsy reveals only focal plasma cell infiltrates around small clumpings of the organisms.

Between birth and the fourth or fifth month of life, the infant's body responds to antigenic challenges, principally with IgM antibody production, later on with IgG. Unless a clear distinction between focal and

interstitial plasma cell pneumonias and other infections is made, an analysis of immunoglobulin levels will lead to non-specific results. In our series a general elevation of all immunoglobulins can be detected, which is not significantly different in pneumocystic and non-pneumocystic infants (Fig. 1). There is a noticeable elevation of all immunoglobulin levels as compared with normal American infants of the same age group due to the frequent and various infections amongst the orphanage infants. The wide range with several cases with extremely low levels may be related to malnutrition and protein loss (Creamer *et al*, 1970; Dutz, Sadri, Kohout, Post, and Bandarizadeh, 1970).

Infants with severe respiratory symptoms, diffuse rapid clouding of the x-ray picture, and all pathognomonic changes of acute interstitial plasma cell pneumonia as well as those showing massive disease at necropsy are found exclusively amongst the highest values of the IgM range (Figs. 2 and 4). Three cases showed elevations of more than 2 standard devia-

Fig. 1 IgM levels in orphanage.

Fig. 2 Summary of immune response in case of Pneumocystis carinii infection with plasma cell pneumonia.

tions. The elevation of the IgM levels is directly related to the amount of plasma cell infiltrate as judged by those cases necropsied as well as by observation of the radiological density of the infiltrate in cases which later were proven serologically. This is most important, since we know of no other disease in this age group which would produce a similar intense plasma cell response. The peak values of IgM can only be detected during a short and limited time period (Figs. 2 and 4). The peak levels are reached two to three days after the crisis followed by a rapid fall. This explains the paucity of well studied cases of interstitial plasma cell pneumonia, since it is difficult to obtain sera at the right moment. Our studies with fluorescent IgM confirmed the findings of Brzosko *et al* (1967) and revealed a very marked increase in intraalveolar and plasma-cellular IgM in cases of acute interstitial plasma cell pneumonia.

IgG levels show on superficial examination similar patterns in interstitial and focal plasma cell pneumonia and nonpneumocystic infants (Fig. 3). Infants with massive interstitial plasma cell pneumonia are, however, found at the lowest level of the range with IgG values of less than 200 mg%. This corresponds to the experiences in experimental pneumocystosis as well as adult pneumocystosis, where hypoergic, hypimmune pneumocystosis develops in severely immune-depressed individuals. The low infantile IgG levels are related to prematurity, atrophy of the bowel mucosa, and marasmus. The complement-fixation test remains negative during this period of high IgM and low IgG levels.

Fig. 3 IgG levels in orphanage.

The survivors respond by the fifth to sixth month of life with an increase in IgG levels indistinguishable from the reaction to infections other than pneumocystosis, except by the concomitant positive complement-fixation test. The titre of the complement-fixation test parallels the quantitative levels of IgG rather than IgM and the complement-fixing antibodies are therefore probably of the IgG type. Tests are occasionally positive in newborns with transferred IgG from the mother, rapidly turning negative. Positive reactions are not detected during the second to fifth month of life (Post, Fakouhi, Dutz, Bandarizadeh, and Kohout, 1971) which means that antibody against *Pneumocystis carinii* is negligible. Serological reactions for *Pneumocystis carinii* are negative in all cases of hypoergic hypimmune pneumocystosis (Goetz, 1966; Robbins, 1968; Fischer, Becker, Joist, and Tismer, 1969) since the naturally occurring IgG response seen in infants is artificially prevented for therapeutic reasons or does not occur due to congenital immunoglobulin deficiency syndromes. Recurrences of pneumocystosis have been observed in cases of hypoergic hypimmune pneumocystosis but never in interstitial or focal plasma cell pneumonia (Frenkel, 1968).

The determination of serum IgA levels in orphanage children from Shiraz showed on average an increase over the normal American levels (Fig. 4). Three of our cases showed a marked sudden drop in IgA preceding a respiratory crisis by two to three days. None of the other IgA determinations in our series was performed during this unpredictable period of time shortly before the massive spread of pneumocystis through the alveoli of the lung. Determinations of fluorescent IgA on two lungs with acute interstitial plasma cell pneumonia showed complete absence of alveolar IgA.

Fig. 4 IgA levels in orphanage.

Cases of adult or infantile hypoergic hypimmune pneumocystosis show either low or normal serum IgA levels (Robbins, 1968). They are frequently associated with a complete absence of the alveolar lining and fibrin membrane formation or severe abnormalities of the lining cells with giant cell formation and alveolar cell degeneration as in inclusion body virus disease and after busulphane therapy. One of the authors (W. Dutz) examined the lungs of 36 cases of hypoergic hypimmune pneumocystosis in the USA related to various immunosuppressive drug regimes or congenital immune deficiencies. Serum IgA levels were invariably low when the alveolar lining was intact. In cases associated with alveolar cell degeneration the serum IgA levels were either normal or low.

IgA is produced by plasma cells, coupled and secreted by epithelial cells to provide surface immune protection (South, Warwick, Wollheim, and Good, 1967; Tomasi and Czewinski, 1968; Martin, 1969; Heremans, 1969). IgA is frequently absent in severe sprue (Heremans, 1969). The invariable association of severe intestinal atrophy with a sprue-like histological pattern (Creamer *et al*, 1970) appears to be of added interest. Although all our findings suggest and point to an absence of alveolar IgA as a prerequisite to the proliferation of this surface spreading parasite, definite clarification of the problem will only be derived from bronchial IgA determinations in affected patients.

We would like to propose from our findings the following hypothesis of the development of interstitial plasma cell pneumonia which is summarized in Figure 4. Complement-fixing antipneumocystic antibodies are transferred to the infant with maternal IgG. The levels of these passively transferred immunoglobulins drop to less than 200 mg% by the third or fourth month after birth, due to natural degradation. This drop is more pronounced in premature infants in whom the interval between birth and immuno-competence is prolonged and aggravated by intestinal infections with sprue-like atrophy of the mucosa and marasmus. The low IgG is the precondition for the intraalveolar proliferation of *Pneumocystis carinii*. Normally IgA prevents surface infection. If serum IgA is absent, alveolar IgA secretion ceases, or the alveolar cells are severely damaged, sudden, explosive, logarithmic proliferation of pneumocystis occurs. The highly antigenic capsules elicit a massive interstitial plasma cell response and IgM antibody formation. The infants die of an alveolar capillary block or survive, the organisms disappearing from the alveoli within a week. The plasma cell infiltrate persists, gradually diminishing in amount over several months and is responsible for the slow resolution of the radiological

opacities. The active formation of IgG antibodies starts at the fifth, and reaches its peak at the ninth month of life. Complement-fixing antibodies show their highest titres during this period.

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