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Clinical conditions associated with positive complement fixation serology for *Chlamydiae*

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SUMMARY

The hospital records of 242 patients with diagnostic chlamydial complement fixation (CF) titres (seroconversion and/or titre $\geqslant 64$) found among 60000 patients screened for suspected viral illnesses were reviewed to study the clinical conditions associated with positive CF serology for *Chlamydiae*. After excluding typical genital *C. trachomatis* infections, the majority of the remainder were considered to represent *C. psittaci* infections. Respiratory symptoms were the most common clinical manifestations of chlamydial infections detectable by CF, but the majority (58%) of the patients did not have pneumonia. Abdominal, neurological as well as urinary tract symptoms were common. Cutaneous, joint, cardiac, genital and ocular manifestations were also noted. Fever ($\geqslant 38{\cdot}5$ °C) was present in 62% of the patients. The ESR was raised ($\geqslant 20$ mm/h) in the majority of the patients (83%), but the leucocyte count was usually (86%) within normal limits. Because the clinical spectrum of *C. psittaci* infections is apparently broad, serological tests for detecting antibodies to *C. psittaci* (e.g. CF) should be used widely in various clinical conditions and not for patients with pneumonia alone.

INTRODUCTION

Chlamydiae are obligate intracellular micro-organisms and common pathogens. *Chlamydia trachomatis* has been intensively studied, and the recognized clinical spectrum of human *C. trachomatis* infections continues to expand. However, infections caused by *C. psittaci*, the other species of the genus, have been neglected, although its importance in many avian and lower mammalian infections is well known (Storz, 1971). Recently, a new *C. psittaci* strain, the TWAR agent, has been discovered as a frequent cause of respiratory tract infections (Grayston *et al.* 1986).

Human *C. psittaci* infections are nearly always diagnosed serologically because facilities for isolating *C. psittaci* are only rarely available. The conventional complement fixation test (CF) thus remains the only practical diagnostic method. The CF test detects genus-specific chlamydial antibodies elicited both by *C. trachomatis* and *C. psittaci* infections, but it has been found useful only in systemic

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infections due to its poor sensitivity. In man, *C. psittaci* infection is usually considered to be a respiratory disease of variable severity (Macfarlane & Macrae, 1983). A variety of extrapulmonary manifestations can, however, accompany the respiratory symptoms. We present a study of the hospital records from 267 patients with diagnostic chlamydial CF titres in which we paid special attention to the clinical and laboratory data.

PATIENTS AND METHODS

Study population

Serum samples from about 60000 persons with suspected viral infections were sent to the Department of Virology, University of Helsinki between January 1975 and March 1981 (a period of $6\frac{1}{4}$ years) for serological investigation. The initial presentations were classified as follows: 26% had respiratory symptoms, 12% abdominal symptoms, 12% fever of unknown origin, 9% neurological, 7% cutaneous, 5% eye or ear symptoms. Serological screening was done by complement fixation (CF) using microtitre plates (Riski *et al.* 1977). The 16–18 antigens used were mostly viral (influenza A and B, parainfluenza 1 and 3, respiratory syncytial, corona, mumps, measles, adenovirus, rotavirus, coxsackie B5, polio, herpes simplex, varicella-zoster, cytomegalovirus) (Ukkonen *et al.* 1984) but included also ether-acetone-extracted group-specific CF antigen from *C. trachomatis*, serotype D, kindly provided by Dr C. Mordhorst, State Serum Institute, Denmark, as well as *Mycoplasma pneumoniae* and *Toxoplasma gondii* antigens. In the CF test a fourfold or greater rise in titre or titres $\geqslant 64$ were considered to be diagnostic of recent chlamydial infection (Schachter, 1986).

Altogether 409 patients (0·7%) had diagnostic antibody titres against the chlamydial CF antigen. The records of these patients were requested from the hospitals concerned and were obtained for 267 patients. To eliminate the effects of other possibly coincidental infections, all those patients from whom other pathogenic microbes had been isolated and/or who had demonstrable rises in antibody or diagnostic titres against other probably causative microbes were excluded from further analysis. The remaining 242 patients were considered to have had a chlamydial infection, and formed the study population.

Statistical methods

Statistical analyses were performed with Student's *t* test.

RESULTS

Age distribution

The age distribution of the patients is shown in Table 1. When compared with the age distribution of all the patients whose sera had been sent for viral serological screening, this material included a statistically significantly lower proportion of infants and children (under 6 years of age), an approximately equal proportion of older children and adolescents, but more young adults (21–30 years of age), middle-aged (31–50 years of age) and old people (over 60 years of age).

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Table 1. *The age distribution of the 60000 patients whose sera were sent for serological CF screening and the 242 patients with diagnostic chlamydial CF titres*

Age/years	With diagnostic chlamydial CF titres (%)	Of all patients whose sera were sent for CF screening (%)
0–6	3	20***
7–10	2	5*
11–20	10	10
21–30	23	16**
31–40	17	13*
41–50	18	11***
51–60	7	11*
61–	20	15*

The asterisks indicate the levels significance: * $P < 0{\cdot}05$, ** $P < 0{\cdot}01$, *** $P < 0{\cdot}001$.

CF titres

Seroconversion in chlamydial CF titres was found in 46 % of the patients from whom paired sera were available (81 out of 177 patients). Of the remainder (those patients without seroconversion; $n = 161$), 40 % had a peak titre of 64, 43 % had 128, 13 % had 256, 4 % had 512 and 1 % had 1024.

Clinical findings

Table 2 summarizes the clinical symptoms and diagnoses of the patients.

Fever. Fever ($\geqslant 38{\cdot}5$ °C) was recorded in 150 patients (62 %); in one third the fever persisted for over 2 weeks.

Respiratory symptoms. Respiratory symptoms were commonest; 150 of the 242 patients (62 %) had some respiratory involvement, and pneumonia was radiologically confirmed in 102 patients. Chlamydial infant pneumonitis was diagnosed retrospectively in three infants by low but fourfold rise in titres (< 8–32, 8–32 and 16–64). A few cases (13) presented with sinusitis (5 %). Tuberculosis was suspected in five cases; only two of these were, however, confirmed by culture (and these two have not been included in the figures shown).

Abdominal symptoms. Various abdominal symptoms were noted in 64 cases (26 %). Nineteen young women were suffering from right-upper-quadrant pain resembling perihepatitis (8 %). Vague abdominal pain and vomiting were quite common (10 and 7 %, respectively).

Neurological symptoms. Forty-two patients (17 %) had neurological symptoms, of which severe headache was the most common (12 %). Seven cases (3 %) had meningitis and two encephalitis (< 1 %). Three patients (1 %) had diplopia.

Urinary tract symptoms. Various urinary tract symptoms were documented in 42 cases (17 %). Haematuria and/or proteinuria and/or pyuria were noted in 11 cases (5 %) and attributed to urinary tract or genital infections. In 25 cases (10 %) no specific reason (other than chlamydia) could be found. These symptoms were, however, mainly transient. Nephritis or glomerulonephritis was diagnosed in six patients (2 %), four of which were confirmed by biopsy. In one patient an

Table 2. *Clinical findings and diagnoses of the 242 patients with diagnostic chlamydial CF titres*

Clinical finding/diagnosis	*n*	%
Fever	150	62
Respiratory symptoms	150	62
Pneumonia	102	42
Bronchitis	19	8
Sinusitis	13	5
Tuberculosis	3	1
Abdominal symptoms	64	26
Perihepatitis	19	8
Vomiting	17	7
Hepatitis	3	1
Pancreatitis	1	<1
Oesophagitis	1	<1
Splenomegaly	1	<1
Peritonitis	1	<1
Non-specific abdominal pain	23	10
Neurological symptoms	42	17
Headache	30	12
Meningitis	7	3
Diplopia	3	1
Encephalitis	2	<1
Urinary tract symptoms	42	17
Non-specific urinary tract symptoms (transient, no urinary tract or genital infection present)	25	10
Nephritis/glomerulonephritis	6	2
Cutaneous manifestations	38	16
Non-specific rashes	16	7
Erythema nodosum	13	5
Arthritides/arthralgias	31	13
Tendinitis	1	<1
Genital infections	25	10
Ocular manifestations	17	7
Conjunctivitis	5	2
Episcleritis	3	1
Keratitis	1	<1
Cardiac symptoms	13	5
Carditis (endo-/myo-/peri-)	4	2
Otitis media	7	3

erythematous rash occured, one had endocarditis, and one suffered from arthralgia of the sacro-iliac joints associated with glomerulonephritis.

Cutaneous manifestations. Skin manifestations were present in 38 (16%), particularly in younger patients (the mean age of the patients with skin manifestations was 35·5 years and 61% of the patients were under 40 years of age). There were 23 women and 15 men in this group. Erythema nodosum was present in 13 cases (5%), and less specific exanthematous lesions in 16 cases (7%). These lesions consisted mostly of small red papules and/or macules. Erythema nodosum was

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most commonly associated with respiratory infection (12 of 13 patients with erythema nodosum also had respiratory symptoms). Nonspecific rash was associated with respiratory infection in eight and with joint symptoms in four cases.

Joint symptoms. Joint symptoms, mainly in the form of arthralgias and reactive arthritides, were recorded in 31 (13%) cases, of which 19 were female and 12 male with 65% of these patients being under 40 years of age. Among these patients respiratory symptoms (including sinusitis and pneumonia) were noted in nine cases.

Others. Genital infections were observed in 25 patients (including 4 cases of lymphogranuloma venereum), ocular manifestations in 17 and cardiac symptoms in 13. Otitis media occurred in 7 cases, 4 of them children with pneumonia. One of the adults, a 49-year-old man, developed otitis media in one ear and sudden deafness in the other after a severe flu-like illness.

Avian contact. The hospital records of only 20 patients (8%) contained a mention of possible contact with birds, and 12 of these admitted having had a bird as a pet or otherwise in close contact (60%).

Laboratory findings

The erythrocyte sedimentation rate (ESR) was markedly raised (> 40 mm/h) in 135 out of 199 patients (68%) and moderately elevated (20–40 mm/h) in 29 out of 199 (15%). Leucocyte counts were within normal limits ($4–10 \times 10^9$/l) in the majority of the patients (86%); 32 (13%) had raised counts while 4 (2%) had decreased numbers. Liver transaminases (SGOT and/or SGPT) were assayed in 125 (52%) of the cases, elevated values were noted in 47 (38%).

DISCUSSION

Infections detected by the CF test may be caused by *C. psittaci* as well as by *C. trachomatis* because the antigen is genus-specific. *C. trachomatis* infections, however, seldom give a sufficiently strong antigenic stimulus to elicit seroresponses detectable by CF. The CF test may also be insensitive for infections with *C. psittaci* and if a CF titre level 64 was used as a criterion CF detected only 21 out of 32 chlamydial pneumonias due to TWAR agent in the studies by Saikku *et al.* (1985), who verified their results by the microimmunofluorescence test. (Saikku *et al.* unpublished data). The presence of concomitant diagnostic titres to other infectious agents among patients with significant CF titres to chlamydia has recently been reported by Nagington (1984). He found that 8·8% of his patients with a diagnostic change in chlamydial CF titres also had serological evidence of infection with other micro-organisms. In our material, screened with a wider assortment of antigens, similar evidence was found in only 4%. A polyclonal B-cell activation caused by *Chlamydiae* (Bard & Levitt, 1984) can be one explanation for this phenomenon, but we have also noted false positive CF reactions in chlamydial antibody determinations. These reactions my be due to the presence of antibodies to various host lipid components in the CF antigen and not to the structural components of chlamydia, but in our experience this phenomenon is not common and does not distort the figures presented here (Saikku *et al.* unpublished data).

Most of the clinical features associated with positive CF serology in this study

have been described in the literature as clinically correlated with *C. psittaci* or *C. trachomatis* infections. We think that, if those patients with clinical findings typical of genital *C. trachomatis* infections are eliminated, the majority of these signs and symptoms are probably due to *C. psittaci* infections. Moreover, genital infections and their complications were found only rarely because samples from these patients were not usually sent for serological screening for viruses.

Respiratory symptoms are considered the most common clinical manifestation of *C. psittaci* infections, and this is evident also in our material. It is, however, worth noting that 58% of these patients did not have pneumonia, as usually thought to be the main manifestation of psittacosis. A few patients (5%) had sinusitis. Jansson (1960) found this syndrome in 9% of patients with ornithosis, and Grayston *et al.* (1986) demonstrated a TWAR infection in some cases of sinusitis. Three cases of chlamydial infant pneumonitis were found in our series, although these infections with *C. trachomatis* are not usually detectable by the CF test (Puolakkainen *et al.* 1984). Although rises in titres were noted in these three infants, the levels were low. On the other hand, over 3600 children under 6 months of age were screened by CF, the majority with respiratory symptoms, and only three cases of chlamydial infant pneumonitis were found although the syndrome is not rare in Finland (Puolakkainen *et al.* 1984).

Thirty years ago a palpable spleen was considered pathognomonic of *C. psittaci* infections (Maclachlan *et al.* 1953) but we could find only one woman with a definite splenomegaly. Nonetheless, other abdominal symptoms were quite common. Perihepatitis, evidently due to *C. trachomatis*, was diagnosed (or suspected) in 19 women (8%), although the sensitivity of CF test in diagnosis of perihepatitis is low (Puolakkainen *et al.* 1985).

The majority of the urinary tract symptoms found in this material were transient and of the type ascribed to febrile infections in general and clearly different from the symptoms seen in venereal *C. trachomatis* urethritis, which seldom causes positive CF reactions (Pasieczny & Sommerville, 1966). Proteinuria and haematuria have been common findings in patients with presumed *C. psittaci* infections (Byrom, Walls & Mair, 1979, Nagington, 1984).

The association between chlamydial CF antibodies and erythema nodosum has been reported in detail by us in a study based partly on this material (Kousa, Saikku & Kanerva, 1980). Both *C. trachomatis* and *C. psittaci* have been implicated in cases of erythema nodosum (Hellerström, 1929; Sarner & Wilson, 1965). Two of the 13 cases of erythema nodosum here were probably associated with *C. trachomatis* because their chlamydial antibody titres measured by indirect immunofluorescence test were substantially higher than those measured by CF (Conway *et al.* 1984). Other cutaneous lesions like erythema marginatum (Simpson, Huang & Grahame-Smith, 1978) or erythema multiforme (Kousa, Saikku & Kanerva, 1980) have been also described in association with chlamydial infections. We noted an association between erythema nodosum and pneumonia, and arthralgias and exanthema, respectively.

C. psittaci infections in animals are often complicated by arthritis (Storz, 1971) but in humans this association is not commonly found, whereas the role of *C. trachomatis* in the etiology of reactive arthritis has been extensively studied (Keat, Thomas & Taylor-Robinson, 1983). A few cases with chlamydiosis and joint

symptoms of variable severity can be found in the literature (Schaffner *et al.* 1967; Simpson, Huang & Grahame-Smith, 1978) and Bhopal & Thomas (1982) have even published a case report of Reiter's syndrome as a presentation of psittacosis. We found arthralgia or arthritis to be common in our patients (13%).

The requirement of a history of contact with birds as a prerequisite for diagnosing *C. psittaci* infections in man has recently been reappraised because cases have been reported without any evidence of the involvement of birds (Saikku *et al.* 1985; Nagington, 1984; Bruu *et al.* 1984; Pether *et al.* 1984). Human-to-human transmission, formerly suggested in family outbreaks (Dalgaard, 1957) and hospital personnel (Broholm *et al.* 1977) cases, seems to be a reasonable mode of transmission for *C. psittaci* infections in man (Grayston *et al.* 1986). In our study, in which contact with birds was not systematically sought and recorded (and perhaps left unrecorded especially if negative, Maffei *et al.* 1984), a presumptive bird source was identified in 63% of those asked but they represented only 8% of the whole material.

More sensitive and more specific serological tests for diagnosing *C. psittaci* infections are needed because the clinical spectrum of the disease is clearly very broad, and because the organism is sensitive to antibiotics. Tests for *C. psittaci* should be used widely in various clinical conditions, and not only for patients with pneumonia who give a history of contact with birds.

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