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Adult onset Still's disease and viral infections

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SUMMARY Several micro-organisms, especially viruses, have been associated with juvenile and adult onset Still's disease. In the present study a search for probable triggering viral infections in five consecutive patients with early, active adult onset Still's disease has been made. In one patient echovirus 7 was identified as a probable triggering agent. Evidence of infection with this virus was acquired by virus cultures and serological tests. In two patients the illness was probably initiated by a rubella reinfection. Both had initially high stable monospecific IgG antibody titres but no IgM antibodies to this virus. In the remaining two cases no particular triggering viral infection could be designated. Evidence of a viral infection was thus found in three of these five patients. Adult onset Still's disease may represent a reaction pattern to certain infections.

Key words: echovirus, rubella, cultures, serology.

Juvenile and adult onset Still's disease are related clinical entities characterised by high spiking fever, an evanescent maculopapular rash, and arthritis.[1 2] Other features frequently found in both conditions include lymphadenopathy, splenomegaly, pericarditis, pleuritis, neutrophil leucocytosis, and hepatic abnormalities. Although the cause of these diseases is unknown, several recent reports have associated their development with a variety of micro-organisms, especially viruses.[3–12]

The present study reports on virological studies performed in five patients with adult onset Still's disease in an early phase of the disease.

Patients and methods

PATIENTS

During 1983 five patients with early, active adult onset Still's disease were seen at two hospitals in the city of Nijmegen, The Netherlands (Canisius-Wilhelmina Hospital, University Hospital St Radboud). All presented with fever of unknown origin and fulfilled the criteria of Medsger and Christy.[13]

METHODS

As soon as it was suspected that a patient was suffering from adult onset Still's disease virological studies were started.

Serology

IgG antibody titres to adenovirus, respiratory syncytial virus, mumps, cytomegalovirus, measles, herpes simplex, varicella, Coxsackie virus B1, 2, 3, 4, 5, and 6, *Coxiella burneti*, psittacosis, and *Mycoplasma pneumoniae* were measured by complement fixation tests, IgG antibody titres to rubella and parainfluenza virus 1, 2, and 3 by haemagglutination inhibition tests, IgG antibody titres to Epstein-Barr virus by immunofluorescence tests, and hepatitis B surface antigen (HBsAg) and IgG antibodies to HBsAg by means of an enzyme linked immunosorbent assay (ELISA). IgG antibody titres to corona virus and influenza virus A, B, and C were measured by complement fixation and haemagglutination inhibition tests. IgM antibodies to mumps, rubella, and parainfluenza virus 1, 2, and 3 were assayed by haemadsorption immunosorbent tests and IgM antibodies to Epstein-Barr virus by immunofluorescence tests.

Virus cultures

All throat swabs and stool specimens were inoculated in Flow 2002 (human lung fibroblasts), HEp_2 (human larynx carcinoma), and primary rhesus monkey kidney cells. Attempts to isolate rubella virus were made only if the IgG antibody titres to

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this virus were 1/512 or less. In these cases throat swabs and urine specimens were inoculated in Vero cells.

Results

Table 1 shows the main clinical and laboratory findings in the five patients with adult onset Still's disease. Table 2 shows the number of days after onset of the disease at which the first and second blood specimens, the throat swab, and the stool specimen were collected in each case. When the first blood specimens for antibody determinations were drawn all patients had normal gammaglobulin concentrations at serum protein electropheresis. None of the sera contained HBsAg or antibodies to HBsAg. Only two of the virus cultures yielded a positive result (Table 3). In patient No 3 echovirus 7 was isolated from a throat swab obtained at day 34 after onset of the illness and from a stool specimen obtained at day 39. Neutralising antibody titres to this virus showed a fourfold increase. During 1983 only one other case of echovirus 7 infection was identified at our virological laboratory.

In patients 1 and 5, high IgG antibody titres to rubella were noted two weeks after onset of the disease (patient 1: 1/2048, patient 5: 1/4096). Similar high IgG antibody titres to rubella were not found in a control group of 48 healthy Dutch blood donor volunteers. Fig. 1 shows the course of the rubella haemagglutination inhibition titres in patients 1 and 5 throughout the study period. During 1983 no epidemic of rubella was observed in The Netherlands.

In the serum of patient 4 high stable IgG antibody titres were detected to no less than five viruses:

Table 1 *Clinical and laboratory findings in the five patients with adult onset Still's disease*

	Patient No				
	1	*2*	*3*	*4*	*5*
Sex	M	F	F	F	M
Age at onset (years)	21	39	36	18	19
Sore throat	+	−	+	+	+
Myalgias	+	+	+	+	+
Fever, 39°C	+	+	+	+	+
Typical rash	+	+	+	+	−
Arthritis	+	+	+	+	+
Lymphadenopathy	+	−	+	−	+
Splenomegaly	+	−	+	−	+
Pleuritis	+	−	−	−	−
Pericarditis	+	−	−	−	+
Maximum ESR* (mm/h)	103	125	128	96	52
Lowest haemoglobin concentration (g/l)	98·2	86·9	109·5	86·9	101·4
Highest leucocyte count $\times 10^{-9}$/l	25·7	12·6	16·8	18·9	14·4
Hepatic abnormalities	+	+	+	+	+
Duration initial attack (months)	9	3	3·5	2·5	1·5
Follow up (months)	24	23	23	23	18

*ESR=erythrocyte sedimentation rate.
+=present; −=absent.

Table 2 *Number of days after onset of the disease at which the first and second blood specimens, the throat swab, and the stool specimen were collected in each case*

	Patient No				
	1	*2*	*3*	*4*	*5*
Blood specimen					
first	14	16	17	26	15
second	43	30	39	54	46
Throat swab	16	39	34	54	46
Stool specimen	16	30	39	54	47

Table 3 *Main virological data for the five patients with adult onset Still's disease.*

Patient	*Virus cultures*	*IgM antibodies*	*IgG antibody titres*
1	−	−	Rubella (1/2048)
2	−	−	—
3	Echovirus 7	−	Echovirus 7 (1/8, 1/32)
4	−	Parainfluenza 1 and 3	Parainfluenza 1 and 3 (1/1280) Rubella (1/2048) Measles (1/256) Adenovirus (1/128)
5	−	−	Rubella (1/4096)

−=low or negative.

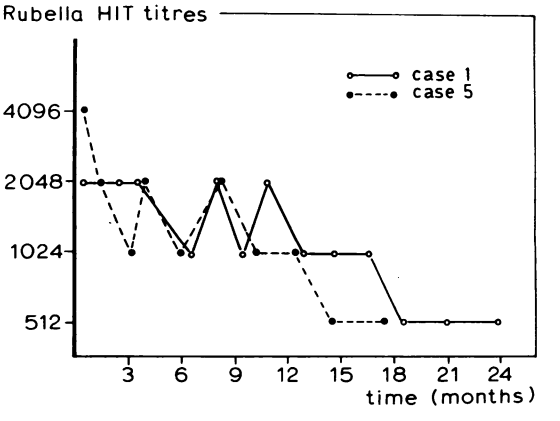

Fig. 1 *Course of the rubella haemagglutination inhibition test (HIT) titres in patients 1 and 5.*

rubella (1/2048), measles (1/256), adenovirus (1/128), and parainfluenza 1 (1/1280) and 3 (1/1280). This patient also had IgM antibodies to the last two viruses. All other serological tests in these five patients showed low titres or negative results. Table 3 summarises the main virological data for the five patients with adult onset Still's disease.

Discussion

During the past 15 years several micro-organisms, especially viruses, have been associated with juvenile and adult onset Still's disease. In seroepidemiological studies of patients with juvenile rheumatoid arthritis raised antibody titres to rubella,[14 15] parainfluenza virus,[16] and Epstein-Barr virus have been found.[16] The significance of these findings was tempered by the discovery that these antibody increases may reflect a general increase in serum immunoglobulins.[15 16] Another approach, as recently reported by Chantler *et al*, has provided much stronger evidence that viruses may play a part in the aetiology of juvenile rheumatoid arthritis.[3] These investigators were able to isolate rubella from lymphoreticular cells in seven of 19 children with chronic arthritis, including one patient with systemic onset juvenile arthritis (Still's disease), 0·5 to 14 years after onset of the disease. In this study no attempts were made to isolate other virus species. Studies performed during the initial phase in nine cases of juvenile or adult onset Still's disease have led to intriguing observations, suggesting that juvenile or adult onset Still's disease can be triggered by rubella,[4–6] Coxsackie virus,[7 8] adenovirus,[7] mumps,[9] *Mycoplasma pneumoniae*,[10] and *Yersinia enterocolitica*.[11] In addition, one recent prospective study indicates that disease exacerbations in patients with juvenile Still's disease are also closely associated with preceding clinical infections, especially of the upper respiratory tract.[12] In this last study herpes simplex (one case), rhinovirus (one case), and streptococcus (three cases) were identified as triggering agents.

The present report shows the results of virological studies performed during the initial phase in five consecutive patients with adult onset Still's disease. In one patient (No 3) it appeared very likely that a viral agent had induced the disease. This patient developed clinical and laboratory evidence of adult onset Still's disease at the time of an echovirus 7 infection. Evidence of this infection was acquired by means of virus cultures and serological tests. So far, only one well documented case of acute polyarthritis ascribed to echovirus has been reported in English publications.[17] This concerns the case of a 35 year old woman with fever, myalgias, and acute polyarthritis in whom echovirus 9 was isolated from throat and rectal swab specimens. The recognition of echovirus infections is hampered by the fact that serological evidence of infection with this virus can be obtained only after virus isolation.

In two patients (Nos 1 and 5) the development of adult onset Still's disease was probably the result of a rubella infection. Both had initially high IgG antibody titres but no IgM antibodies to this virus. In The Netherlands more than 90% of young adults (age 18–21 years) possess IgG antibodies to rubella.[18] Therefore it is much more likely that these patients suffered from a reinfection than from a primary infection. Reinfections with rubella generally evoke a rapid IgG but no IgM response.[19] From this point of view it is not surprising that the first blood specimens in these cases, drawn two weeks after onset of the disease, already showed high titres of IgG antibodies to rubella but no IgM antibodies. Polyclonal stimulation in these cases seems unlikely because none had high IgG antibody titres to the other 25 micro-organisms tested. Moreover, none initially showed evidence of hypergammaglobulinaemia. In other rheumatic diseases, such as rheumatic fever or reactive arthritis, high stable monospecific IgG antibody titres to group A streptococci, yersinia, salmonella, campylobacter, or chlamydia, are generally considered to be of diagnostic value.[20 21]

Rubella reinfections mostly remain subclinical.[22] Nevertheless there is circumstantial evidence that arthritis associated with rubella may occur after reinfections.[23–25] One report suggests that persons suffering from reinfections are even more likely to develop polyarthritis than those with primary infections.[25] As already mentioned, other investigators have found evidence by virus isolation that rubella infections may induce juvenile or adult onset Still's disease.[3 4 6] In the remaining two patients (Nos 2 and 4) no particular triggering agent could be designated. In one of them high IgG antibody titres to parainfluenza 1 and 3, measles, adenovirus, and rubella and IgM antibodies to parainfluenza were noted, compatible with one or more virus infections or polyclonal stimulation, or both. In the other patient no raised IgG antibody titres or IgM antibodies were found.

Most rheumatic diseases are thought to be the result of an interaction between host and environmental factors. HLA studies in patients with adult onset Still's disease have shown an increased prevalence of B14,[26] Bw35,[27] Cw4,[27] DR4,[28] and DR7.[26] The results of the microbiological studies indicate that in three of our five patients viruses may be an important exogenous factor in the development of adult onset Still's disease.

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