Persistent rubella-specific IgM-antibody in the cerebrospinal fluid of a child with congenital rubella

TIMO VESIKARI, OLLI H MEURMAN, AND RITVA MÄKI

Department of Paediatrics, Tampere Central Hospital, and Department of Virology, University of Turku, Finland

SUMMARY Rubella-specific IgM-antibody was detected, using a solid-phase radioimmunoassay (RIA) method, in the CSF of a child with congenital rubella at ages 3 and 4 years. No rubella-specific IgM was found in the CSF of 20 other children with congenital rubella, and the ratios of rubella-specific IgG RIA antibody titres in serum and CSF were normal.

In infants with congenital rubella infection the virus excretion gradually ceases during the first year of life.¹ Persistence of the virus in the lens up to 3 years has been described.² Furthermore, rubella virus antigen has been demonstrated in the thyroid at age 5½ years in a child with congenital rubella.³ Clinically, there are various late onset manifestations in congenital rubella—such as, diabetes, hypothyroidism, and growth hormone deficiency. Viral persistence and reactivation may have a role in these and also in the progressive hearing loss in children with congenital rubella.⁴

The most remarkable late onset manifestation of congenital rubella however, is a slow central nervous system infection resembling SSPE.⁵⁻⁶ These patients had high titres of rubella antibody both in serum and CSF. Therefore the presence of rubella antibody in the CSF may be an indicator of viral persistence or reactivation in the CNS. We looked for rubella antibody in the CSF of 21 children with congenital rubella, and found evidence suggesting prolonged infection in one.

Patients and methods

21 children aged 3 to 12 years with confirmed or suspected congenital rubella were studied. In 5 cases the diagnosis was made during the first year of life by the demonstration of either rubella-specific IgM antibodies or persistent total rubella haemagglutination-inhibiting (HI) antibodies. In the remaining 16 children the diagnosis was first made sero-

logically between 1 and 4 years of age. In addition to demonstrable rubella HI antibodies the children had clinical findings consistent with congenital rubella, and there was a history of suspected or confirmed maternal rubella in pregnancy in 17 cases. Each child had a hearing defect, ranging from slight unilateral to severe bilateral. In fact, many of the older children were detected during a survey for rubella antibody in congenital hearing loss.⁷ Other principal symptoms and signs related to congenital rubella are listed in the Table.

Solid-phase radioimmunoassay (RIA) for rubella antibody. The procedure has been described in detail.^{8,14} Briefly, partially purified rubella virus antigen was absorbed on to polystyrene balls. After incubation with sera or CSF specimens, the attached rubella-specific IgG and IgM antibodies were demonstrated using antihuman γ -chain or antihuman μ -chain antibody labelled with ¹²⁵I. For the demonstration of rubella IgM antibody the specificity of the reaction was checked using a control antigen preparation made from uninfected Vero cells. Furthermore, the IgM-positive specimens were studied for the presence of rheumatoid factor using a RIA method.⁸

Rubella HI titration was done as described previously.⁹ The sera were pretreated with kaolin and absorbed with chicken red blood cells.

The total immunoglobulin (IgG and IgM) concentrations of CSF were determined nephelometrically using commercial antisera (Behringwerke).

Results

19 of the 21 children had demonstrable rubella HI antibody in the serum at the time of study (Table); one of the 2 seronegative children also lacked rubella

Department of Paediatrics, Tampere Central Hospital

TIMO VESIKARI, paediatrician

Department of Virology, University of Turku

OLLI H MEURMAN, virologist

Department of Microbiology, Tampere Central Hospital

RITVA MÄKI, microbiologist

Table Rubella antibodies in serum and cerebrospinal fluid in 21 children with congenital rubella syndrome

Case	Main symptoms*	Age at study (years)	Rubella antibodies			
			Serum		CSF-RIA	
			HI	RIA	IgG	IgM
1	Retinopathy.	3	20	2048	32	32
	Convulsions	4	20	4096	16	8
2	None	3	20	1024	< 4	< 4
3	Retinopathy	3	80	64000	128	< 4
4	Hyperkinetic	4	80	8000	8	< 4
5	Retinopathy	5	10	8000	8	< 4
6	Hyperkinetic	5	20	8000	16	< 4
7	Retinopathy	5	20	2048	32	< 4
8	Retinopathy	8	40	16000	8	< 4
9	None	8	<10	16	< 4	< 4
10	Psychomotor retardation	8	10	64	< 4	< 4
11	Slight paresis	8	80	8000	8	< 4
12	Retinopathy	8	40	8000	4	< 4
13	Retinopathy. Skeletal anomalies	9	40	32000	32	< 4
14	Retinopathy. Slight paresis	9	20	4096	16	< 4
15	Retinopathy. MBD	9	20	4096	16	< 4
16	None	9	<10	<16	< 4	< 4
17	Psychomotor retardation	10	320	8000	16	< 4
18	None	10	10	512	< 4	< 4
19	Retinopathy. Skeletal anomalies	10	80	32000	32	< 4
20	Retinopathy. Microcephaly	11	10	4096	< 4	< 4
21	Psychomotor retardation	12	20	8000	< 4	< 4

*All children had hearing defects.
MBD = Minimal brain damage.

RIA antibody. Both children had had rubella HI antibody several years earlier, at ages 2 years 8 months and 3 years 10 months respectively, and therefore had apparently lost rubella antibody. In the remaining 19 children, the rubella HI antibody titres ranged from 1:10 to 1:320 and the RIA titres from 1:64 to 1:64000. Rubella-specific IgM was not demonstrable by RIA in any of the sera.

Rubella-specific IgG antibody was detected in the CSF of 14 children (Table). There was usually a good correlation between the serum and CSF rubella RIA antibody titres, and the CSF/serum ratio ranged from 1:500 to 1:2000. The total protein of CSF was well within normal limits in each case (range 0.05 to 0.68 g/l). There was no nephelometrically detectable IgM in any of the CSF specimens.

Rubella-specific IgM antibody was found in the CSF in one patient (Case 1, Table). This child had hepatosplenomegaly at birth, but was otherwise without symptoms. At 6 months he had short episodes of convulsions. The ophthalmological examination at this age was described as normal, but at age 1½ years and later, retinal pigmentation

was detected. The hearing defect was also detected when he was 1½ years. There has apparently been no progression of the hearing loss which is moderate and bilateral. The EEG was slightly abnormal at age 3 years, but there were no further neurological symptoms after age 6 months, and the child remains well and appears of normal intelligence.

Attempts at rubella virus isolation at 3 years were made from CSF, from a lymph node biopsy, and from peripheral blood lymphocytes using RK 13 cells. All tests were negative.

The test for rubella IgM antibody in the CSF, first found positive at 3 years, was repeated again 3 months later and again at 4 years. In the first repeat the same titres of rubella-specific IgM and IgG antibody (each 1:32) were found as in the first CSF specimen. By age 4 years the CSF rubella antibody titres had decreased, but there was still some rubella-specific IgM antibody detectable by RIA (Table). There was no reaction with control antigen preparation, and no rheumatoid factor could be detected in the CSF by RIA.

Discussion

This study showed no indication of chronic infection in most children with congenital rubella. However, the finding of rubella-specific IgM antibody in one patient at ages 3 and 4 years suggests that in some patients with congenital rubella the virus may persist in the CNS for years and thus cause continuous antigenic stimulation. Nevertheless, there have been no signs of progressive neurological disease in the patient, and we were unable to isolate the virus from him.

Conceivably, however, a patient with virus-specific IgM antibody in CSF might be a candidate for later reactivation of the virus and possible development of a late onset rubella encephalitis. However, our finding of rubella-specific IgM in the CSF is different from the patients with progressive rubella panencephalitis after congenital rubella at a later age. In the latter cases only IgG class rubella antibody was found in the CSF.¹⁰⁻¹¹ Therefore we think that our case represents the continuous presence of rubella antigen in the CNS rather than reactivation of the virus. A high titre of rubella antibody and a raised concentration of IgM in the CSF was described by Lebon and Lyon in a patient with noncongenital progressive rubella encephalitis.¹²⁻¹³

If the above speculation is right a sensitive and specific method, such as RIA, for the demonstration of rubella-specific antibody in CSF might be useful for two reasons: follow-up of persistence of infectious process in the CNS in cases with congenital

rubella, and detection of possible cases of reactivation at a later age. It is not yet certain whether systematic screening for CSF rubella antibody in children with congenital rubella is recommended.

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Correspondence to Dr T Vesikari, Tampere Central Hospital, Department of Paediatrics, 33520 Tampere 52, Finland.

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