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White Matter MR Hyperintensities in Adult Patients with Congenital Rubella

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PURPOSE: To observe and quantify white matter hyperintensities on MR images in adults with schizophrenialike symptoms who had had congenital rubella, in order to elucidate the neuropathologic sequelae of this perinatal viral infection and to explore the potential relationship of these lesions to schizophrenia. **METHODS:** Eleven deaf adult patients with documented prenatal rubella virus infection and schizophrenialike symptoms were compared with 19 age-matched patients with early-onset schizophrenia who did not have congenital rubella and with 18 age-matched control subjects. All MR images (obtained at 1.5 T) were evaluated by a neuroradiologist who was blinded to diagnosis and were rated for white matter lesions on a five-point scale: 0 = no lesions; 1 = 1 lesion less than 1 mm in diameter; 2 = 1 to 4 lesions 1 mm or greater; 3 = 5 to 10 lesions; 4 = more than 10 lesions or a single lesion more than 1 cm in diameter. In addition, the white matter hyperintensities were volumed objectively with a manual threshold technique. **RESULTS:** Ratings of white matter lesions were significantly higher in the rubella patients than in the control subjects: 6 of the 11 patients had ratings greater than 1 compared with 1 of the 18 control subjects and none of the 19 schizophrenic patients. Also, MR images in five rubella patients received ratings at the highest end of the scale of abnormality (3 or 4). The white matter hyperintensities were characterized as bilateral T2 signal hyperintensities in periventricular and subcortical regions, punctate or linear in shape; they were observed predominantly in parietal lobes. **CONCLUSION:** This quantitative MR study of adult rubella patients disclosed abnormal white matter lesions that may correspond to neurovascular lesions known neuropathologically. They do not appear to be directly related to schizophrenialike symptoms.

Index terms: Brain, magnetic resonance; Nervous system, infection

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Prenatal exposure to the rubella virus may produce a syndrome of central nervous system (CNS) defects; most commonly, hearing loss and psychomotor retardation, and psychiatric disturbance in as many as 50% of cases studied. Although these reports of psychomotor retardation and neurologic abnormalities suggested direct effect of the rubella virus upon the CNS, neuropathologic evidence of this CNS involvement was clarified after the 1964 rubella epidemic, when a number of pathologic studies were conducted. Rorke (1) summarized the prevalence of different abnormalities in 19 studies and concluded that there was abnormality in the cerebral vascular system in more than 50% of the cases. These vascular lesions resulted in ischemic brain damage with foci of necrosis along the path of the damaged brain vessels in both white and deep gray matter. Additionally, microcephaly was common and thought to result from direct inhibition of the rubella virus on cell division (2).

We used magnetic resonance (MR) imaging to study brain morphology in rubella patients with schizophrenialike symptoms and com-

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pared the findings with those of healthy control subjects. Because all the rubella patients had psychotic symptoms and most had symptoms consistent with schizophrenia, we added another comparison group to control for the presence of psychotic symptoms. These patients were drawn from the same state hospital as the rubella patients and had schizophrenia with an early age of symptom onset (age 7 to 21 years old) (see Lim et al [3] and Lim et al [4] for further information on these patients). A previous study of these groups revealed microcephaly, ventriculomegaly relative to head size, and cortical gray volume deficits in the rubella group; the schizophrenic group showed ventricular enlargement and cortical gray matter volume deficits but not microcephaly (3). An unexpected finding was a high prevalence of focal white matter lesions in the adult rubella patients, which is the basis of this article.

Subjects and Methods

All subjects or their conservators gave written informed consent.

Patients with Congenital Rubella and Schizophrenialike Symptoms

Eleven patients with congenital rubella and psychiatric symptoms were recruited from the Napa State Hospital Inpatient Service. These patients, nine men and two women aged 20 to 32 years old (mean, 25 ± 4 years), had a documented history of congenital rubella and perinatal deafness. Typically, they could not be managed at home because of violent or antisocial behavior. On average, the Global Assessment Functioning Scale score was 38 ± 26, where 100 represents the best level; Weschler Adult Intelligence Test–Revised performance IQ ranged from 55 to 115 (mean, 82 ± 19). Seven patients had a positive maternal history of characteristic rubella rash and four had substantial signs and symptoms of the congenital rubella syndrome with a history of maternal exposure. The patients were classified by means of the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders–Revised Third Edition (DSM-III-R) (5, 6) through clinical examination and chart review. Although the presence of rubella precluded psychiatric diagnosis, the rubella patients had symptoms that were consistent with DSM-III-R criteria for the following diagnoses: schizophrenia (n = 7), schizoaffective disorder (n = 1), bipolar disorder plus obsessive compulsive disorder (n = 1), obsessive-compulsive disorder (n = 1), and antisocial personality (n = 1). All had sensorineural hearing deficit. Typical clinical symptoms were socially inappropriate behavior, violent rages, obsessions and compulsions, and thought disorders.

Patients with Schizophrenia

All 19 patients were drawn from Napa State Hospital and met DSM-III-R criteria for schizophrenia (see Lim et al [3] for further description). This group was matched in age to the rubella group and comprised 19 men with an early or typical symptom onset (mean age, 15 ± 3 years; range, 7 to 21 years). On average, these patients had 9 ± 3 years of education; verbal IQ was 77 ± 18; and total Brief Psychiatric Rating Scale score, which assesses psychiatric symptom severity, was 56 ± 12.

Healthy Control Subjects

The control subjects included 18 men, age-matched to the rubella group (mean age, 27 ± 4 years; range, 21 to 32 years; years of education, 16 ± 3; range, 12 to 20). These subjects, described previously (3, 4, 7), underwent rigorous screening procedures that excluded subjects for history of medical or neurologic illness or trauma that would affect the CNS; and current or past psychiatric and nonalcoholic drug-use problems. Screening included a psychiatric interview, medical history, physical examination, and a panel of blood tests (complete blood cell count, screening chemistry panel) administered at the time of MR imaging.

MR Acquisition

All subjects were scanned using 1.5-T scanners according to imaging parameters and procedures described previously (8, 9). Axial MR images were acquired using a spin-echo sequence with a field of view of 24 cm and a 256 × 256 matrix. Acquisition was gated to every other cardiac cycle for an effective repetition time of more than 2400 milliseconds with one excitation for each of 256 phase encodes. Early and late echoes were obtained at 20 and 80 milliseconds, respectively. All axial images were oriented in an oblique plane, perpendicular to the sagittal plane, and passing through the anterior and posterior commissures, which were identified from a midsagittal image. Beginning inferiorly at the base of the pons, 17 to 20 sections were collected, each 5 mm thick, with a 2.5-mm intersection skip to reduce crosstalk.

Coronal images also collected at this time included 22 contiguous 3-mm-thick sections oriented perpendicular to the anterior commissure/posterior commissure line. Images were acquired using a multiecho, flow-compensated, cardiac-gated pulse sequence (≈2800/40, 80/1 [effective repetition time/echo time/excitations]) with field of view of 24 cm, and a 256 × 256 matrix. A scout midline sagittal image was used to determine the anterior commissure/posterior commissure line and to define the anterior and posterior limits of collection. Image acquisition was specifically designed to encompass temporal-limbic structures, beginning 6 mm anterior to the anterior commissure and extending 66 mm posteriorly (10, 11).

MR White Matter Signal Hyperintensities

Ratings. All scans were reviewed by a neuroradiologist to exclude cases with space-occupying lesions or other gross structural abnormalities. A second blinded review of all patients and control subjects was then performed in order to analyze the extent of white matter hyperintensities. For this analysis, both axial and coronal images were reviewed and rated according to a scale modified from van Swieten et al (12). On a five-point scale, these lesions were graded as follows: 0 = no lesions; 1 = 1 lesion less than 1 mm in diameter; 2 = 1 to 4 lesions 1 mm or greater; 3 = 5 to 10 lesions; 4 = more than 10 lesions or a single lesion more than 1 cm in diameter.

Quantification. In a second analysis, all areas of signal hyperintensity were manually thresholded at the computer monitor by applying a tint to the hyperintense pixels. The absolute volumes of the white matter hyperintensity pixels, expressed in cubic centimeters, formed the basis of the quantitative analysis and were derived by summing the white matter hyperintensity pixels across all the sections on which they appeared.

Statistical Analysis. For quantification based on the five-point rating scale, group comparisons were tested with nonparametric statistics, including the Kruskal-Wallis test and the Mann-Whitney *U*-test. Correlational analyses were performed with Spearman rank correlations. For MR quantification based on volume estimates, nonparametric statistics were also used to test group comparisons because of the difference in distributions of these estimates across the groups.

Results

White matter hyperintensities were seen in 6 of the 11 rubella patients, in none of the 19 schizophrenic patients, and in only 1 of the 18 control subjects (Fig 1, top). This single control subject had a rating of 1, indicating a single lesion less than 1 mm in diameter. Five of the rubella patients had ratings of either 3 or 4. The difference between the control and the rubella group was significant ($Z = 3.06$, $P = .0022$). These ratings were not correlated with age ($\rho = .16$, not significant), or head size ($\rho = -.41$, not significant).

Figures 2 and 3 are examples of rubella patients with white matter hyperintensity ratings of 4. The white matter hyperintensity appeared as punctate, ovoid or linear hyperintensities on T2-weighted images in the subcortical or periventricular regions, observed predominantly in the parietal and frontal lobes.

White matter hyperintensity quantification was based on raw volume scores expressed in cubic centimeters (Fig 1, bottom). The white matter hyperintensity volumes of the 11 rubella patients correlated significantly with the white matter hyperintensity ratings ($\rho = .975$, $P < .0021$). On average, the rubella group had significantly greater volume of white matter hyperintensity than did the control group ($Z = 3.083$, $P = .0021$); because the schizophrenic group had no white matter hyperintensity, their average white matter hyperintensity volume was 0. Neither age nor head size was a significant correlate of white matter hyperintensity volume in the 11 rubella patients (age: $\rho = .26$, not significant; head size: $\rho = -.21$, not significant). Correlations performed to assess the association between the white matter hyperintensity raw volumes and the cortical ($\rho = .32$, not significant) and ventricular ($\rho = .31$, not significant)

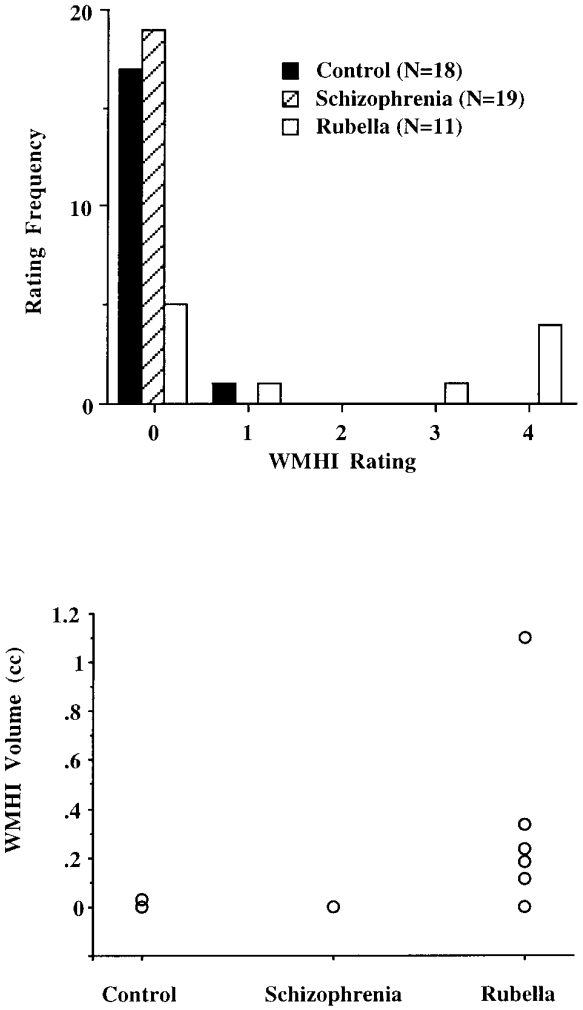


Fig 1. *Top*, Frequency of white matter hyperintensity (*WMHI*) rating for each subject group.

Bottom. White matter hyperintensity (*WMHI*) volumes (in cubic centimeters, *cc*) for each subject in each group. Values of zero are overlapping.

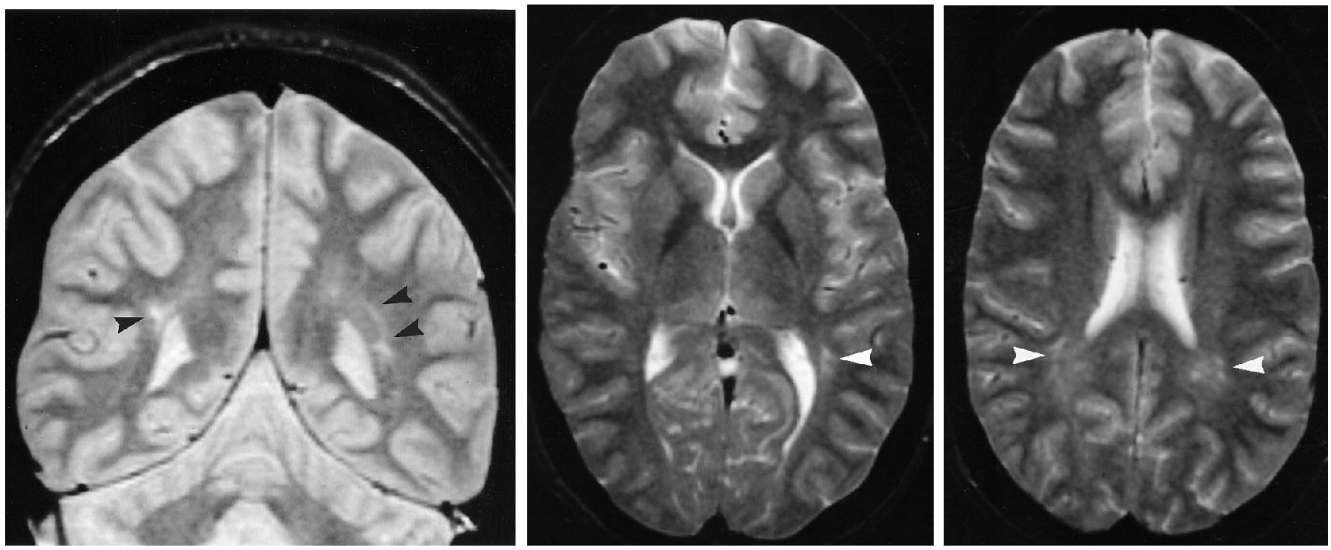


Fig 2. MR images of a rubella patient with a rating of 4 on the white matter hyperintensity scale.

A, Coronal proton density–weighted image (2800/40) shows multiple foci of linear and punctate high signal intensity in the deep white matter adjacent to the trigones of the lateral ventricles (*arrowheads*).

B and *C*, T2-weighted axial images (2769/80) show multiple foci of high signal intensity in the deep white matter adjacent to the trigones of the lateral ventricles (*arrowheads*).

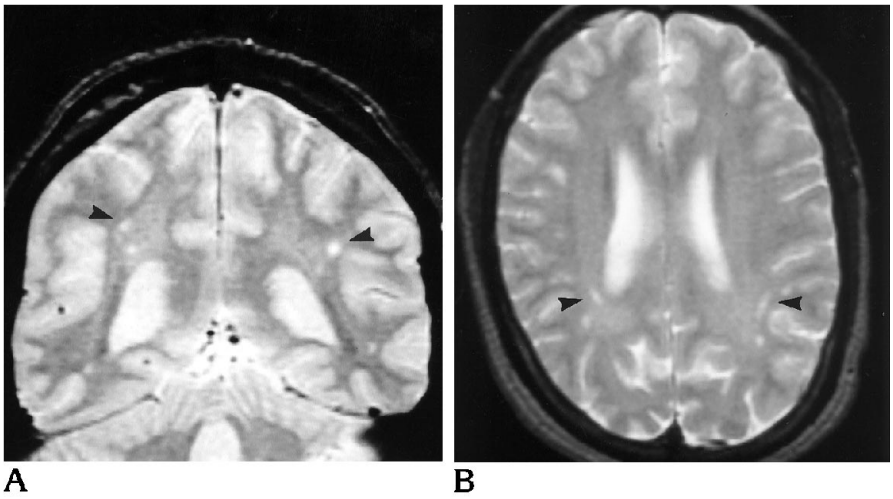
raw volumes, derived from our previous study (3), yielded no significant results in these patients.

Discussion

Few imaging studies have been done of adult survivors of congenital rubella. A CT study of five children found low density in deep white matter as well as multiple calcified nodules (13). Abnormalities have also been reported on cranial sonograms (14, 15). One MR study showed periventricular and subcortical hyperintensities and delayed myelination in one of two children with rubella (16). Frontal and parietal white matter lesions in two children with congenital rubella and severe neurologic deficits have also been documented (17). The present study revealed focal hyperintensities on MR images in more than 50% of adult survivors of congenital rubella who had schizophreniclike symptoms, with an almost nonoverlapping prevalence in age-matched control subjects. The white matter hyperintensity observed in the

Fig 3. MR images of another patient with rubella, also with a rating of 4 on the white matter hyperintensity scale.

A and *B*, Coronal proton density–weighted image (2800/40) (*A*) and axial T2-weighted image (3051/80) (*B*) show bilateral multiple punctate foci of high signal intensity in the subcortical and periventricular regions bilaterally (*arrowheads*).



rubella patients could not be correlated with the presence of schizophrenia symptoms because the matched group of schizophrenic patients, who were free from congenital rubella, had no white matter hyperintensity. These white matter hyperintensities appeared as a pattern of multiple bilateral linear or punctate lesions, predominantly in the deep white matter of parietal and frontal lobes.

Many neuropathologic studies have been performed with infants who have died of congenital rubella syndrome. The most common abnormality involved the cerebral blood vessels, with focal areas of destruction of the walls of arteries and veins accompanied by granular debris in the damaged walls, pericapillary collections of the amorphous granular material, and thickening and proliferation of the walls resulting in narrowing of the lumina. Although blood vessels of all types were involved, the most frequently affected were the penetrating vessels in the deep white matter and the basal ganglia. Associated with these vascular abnormalities were frequent foci of ischemic necrosis, occasionally with small associated cysts (1).

The rubella patients in our series were all young adults who had survived the illness, and it is not known whether this group of patients would have had the same cerebral vascular lesions previously documented in nonsurviving infants. Nonetheless, the location of these lesions in the deep white matter, their punctate and linear configuration, and their high prevalence all suggest that they may represent the ischemic sequela of periarterial and pericapillary degeneration in the deep white matter that is a direct effect of the rubella virus.

Finally, this study suggests that these white matter lesions have no relationship to the schizophrenialike symptoms in these patients. It would be of interest to perform an MR study in a group of rubella survivors without psychiatric illness to determine whether they also show an increased prevalence of these lesions. We intend to extend our investigations to include such a group in the future.

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