reactions when given either intradermally or subcutaneously. Insulin carrier media (Novo) did not induce a reaction.

Four separate attempts were made at desensitisation with parenteral insulin using either rapid³ or slow⁴ desensitisation schedules, but these were unsuccessful. Antihistamines (chlorpheniramine 4 mg four times daily by mouth or 5 mg subcutaneously with insulin injections; cimetidine 200 mg three times daily by mouth or 100 mg subcutaneously with insulin injections) and dexamethasone 0.5 mg with each injection for three days were without effect. Two days of prednisone 20 mg daily was without benefit. Long term, higher dose steroids were not given because of their likely effect on the diabetes and their unsuitability for long term management.

Finally, desensitisation was attempted using oral insulin together with non-steroidal anti-inflammatory agents to antagonise vascular mediators of the reaction. Regular insulin, 800 U by mouth three times daily before meals, and enteric coated aspirin (Rhusal, Roerig), 1300 mg three times daily, were given for one week. Desensitisation was then carried out successfully using neutral insulin (Actrapid MC). Over the next six months he had very occasional swellings at the site of injection without pain or itch. He then stopped aspirin voluntarily and within a few days the original allergic reactions returned. Aspirin 1300 mg twice daily again reduced reactions to once every one or two weeks and was continued permanently. Diabetic control assessed by home monitoring of capillary blood glucose values was excellent, with mean glucose concentrations of 7.8 mmol/l (126-144 mg/100 ml).

Comment

Cutaneous allergy to insulin resistant to standard desensitisation measures is rare.¹ Although desensitisation by parenteral means has been widely used in patients sensitive to inhalant

allergens, the oral approach to desensitisation has been much less studied. There is only trivial absorption of oral insulin, and desensitisation by this route may not require systemic absorption of the allergen. In our patient oral desensitisation alone proved insufficient to control the allergy, so that full control and long term remission was achieved only with the addition of aspirin. It is indeed uncertain whether oral desensitisation was necessary. Non-steroidal anti-inflammatory drugs have a broad range of action and might readily affect local vascular changes concerned in the allergic process and so explain the results seen in this patient. Whatever the mechanism, the present approach provided a simple method for treating a difficult clinical condition.

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Retrospective diagnosis of congenital rubella

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Abstract

One hundred and five children and adolescents with impaired hearing and 19 with impaired vision underwent in vitro tests (lymphocyte responsiveness and serum antibody to rubella) for retrospective diagnosis of intrauterine rubella. Tests yielded results consistent with intrauterine rubella in 30 (29%) of the patients with impaired hearing but only one (5%) of those with impaired vision. In addition, the reported incidence (10.8%) of rubella as a cause of deafness was obtained by questioning parents before the tests. Of 27 patients with impaired hearing of unknown aetiology but reported rubella contact during the pregnancy, seven (26%) had test results consistent with intrauterine rubella.

The incidence of intrauterine rubella as a cause of deafness is probably underestimated when the diagnosis is based on the presence of several classic features.

Introduction

For over a century rubella (or German measles) was considered to be a mild disease. Then in 1941 the intrauterine effects of rubella were recognised.¹ By 1943 maternal rubella during pregnancy was documented as being associated with deafness, blindness, heart disease, and other congenital malformations among infants.² In 1969 Cooper *et al*³ estimated that the incidence of fetal damage after maternal infection in the first trimester of pregnancy was "in excess of 20%." These results were confirmed by Miller *et al*,⁴ but the numbers in their study were small.

The diagnosis of intrauterine rubella is easy to confirm in infants born with several classic features of the disease.⁵ In other children affected by rubella the clinical diagnosis may be impossible, particularly in those infected later in pregnancy whose only clinical feature may be nerve deafness, which will not be diagnosed in infancy at a time when viral culture can offer confirmation.⁶

In 1979 Buimovici-Klien *et al* showed that lymphocyte transformation after stimulation with phytohaemagglutinin was significantly lower in children with congenital rubella than in healthy controls.⁷ Specific lymphocyte responses to purified rubella virus were absent or at least two times lower in children with congenital rubella than in immune controls. In 1981 workers at this laboratory investigated these claims. The results obtained led to the development of a useful diagnostic test, using readily available reagents, to measure the immunological responses to rubella virus antigens in vitro.⁸ Lymphocytes from

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those children whose deafness was due to rubella and who had rubella antibodies were unable to respond in vitro to rubella antigen. In contrast, lymphocytes from antibody positive controls and patients whose deafness was due to other causes responded to rubella antigen in vitro if they had serum antibody. This test could thus differentiate patients whose deafness was due to intrauterine rubella from those whose nerve deafness was due to other causes.

In 1971 Cooper *et al* showed a more rapid drop in haemagglutination inhibition antibody titres in children with congenital rubella than in children infected with rubella after birth.⁹ Of the children they studied, 18.5% were seronegative by 5 years old. Most such seronegative children with the congenital rubella syndrome did not seroconvert when immunised with rubella vaccine. In contrast, a 98% incidence of seroconversion was found in normal children.⁹ The lack of seroconversion after immunisation in children with congenital rubella permitted differentiation between patients with intrauterine rubella and a loss of antibody titre and patients who had been neither infected postnatally nor immunised.

In this study we used these assays in a large cohort of children with nerve deafness to determine the relation between the aetiology of hearing impairment as seen by parents and the results of our tests.

Patients and methods

We investigated 105 patients with nerve deafness (median (range) age 9 (3.5-20) years). They were recruited through various clinics, schools, and associations for people with impaired hearing. All those who volunteered after a request to take part in the study were tested whether or not the aetiology of their hearing impairment was known. Hearing impairment was sufficient in all instances to require the wearing of a hearing aid.

Parents were asked what they thought or what they had been told was the cause of their child's hearing impairment and what evidence was available to support that diagnosis. They also answered a questionnaire about the other lesions associated with intrauterine rubella and about a family history of deafness. Medical records were obtained where possible. Mothers were asked about contact with rubella during pregnancy, problems that occurred throughout the pregnancy, at birth, or during the postnatal period, a family history of hearing loss, and feedback from doctors attending to their child. Children were defined as "rubella probable" on the basis of suspected rubella contact during the pregnancy and a supporting diagnosis made by a medical practitioner or laboratory test or "rubella possible" on the basis of suspected rubella contact during pregnancy but no other complete supporting data or data, such as familial deafness, that would permit the rejection of intrauterine rubella as the cause of deafness. Physical and audiometric examinations were not performed as part of this study; these examinations had been performed previously in all patients.

Nineteen patients (median (range) age 12 (8-20) years) from a clinic for the visually handicapped were also tested.

Testing required 20 ml of blood to be taken from each patient. Each patient's rubella antibody state and in vitro lymphocyte response to rubella antigen were determined initially. In some cases a further 1 ml of blood was required six to 10 weeks after immunisation with Cendevax to determine the patient's antibody state after immunisation.

Culture of lymphocytes—Mononuclear cells separated by Ficoll sodium metrizoate density gradient centrifugation were cultured in the presence of dilutions of rubella complement fixation antigen or rubella control antigen (Flow Laboratories). The technique used was that described by Hosking *et al*.⁸ From the data reported by Hosking *et al*⁸ the cut off point for a positive stimulation index was taken to be 3.2. A known positive control test was performed in parallel with each batch of tests on patients' blood samples. Controls were chosen from healthy members of staff previously tested and found to give positive in vitro lymphocyte culture and to have serum antibody to rubella antigen.

Rubella antibody titres—Serum antibody titres were determined by the single radial haemolysis technique (Rubazone, SRH, Sydney). Results were expressed as international units of rubella IgG antibody present in the serum tested.

Rubella vaccination—To differentiate between a person who had not had a rubella infection and a patient with intrauterine rubella whose antibody titre had dropped below baseline levels, Cendevax (Smith,

Kline, and French Laboratories, Sydney) was administered to all patients with a negative rubella antibody titre and negative in vitro lymphocyte stimulation result. Blood was obtained for measurement of rubella antibody six to 10 weeks after immunisation.

Statistical analysis—Significance was evaluated by the Mann-Whitney U test or the χ^2 test of association and, when appropriate, Fisher's exact test.

Results

To assess whether the in vitro lymphocyte response after immunisation was equivalent to that after natural infection a group of 13 naturally infected controls was compared with a group of six controls who were known to be antibody negative before immunisation with Cendevax. Blood for lymphocyte responses was obtained from the second group at least six weeks after immunisation. The naturally infected controls had significantly higher responses (median 6.7, range 4.5-20.0) than the immunised controls (median 2.6, range 1.3-3.8) ($p < 0.002$), showing that an immunised control could easily be mistaken for a patient with intrauterine rubella—that is, he or she would have antibody but could well have a lymphocyte response that was below the positive/negative cut off point. Because of these findings we were unable to classify 15 patients (table). As they could have been either rubella positive or rubella negative they were omitted from further calculations.

Number (%) of patients in whom rubella tests yielded positive, negative, or uncertain results

Clinical diagnosis	Rubella tests		
	Positive*	Negative†	Uncertain‡
Impaired hearing:			
Rubella probable§	11 (85)	2	4
Rubella possible	7 (26)	20	1
Rubella unlikely or data not available	12 (18.5)	53	10
Total	30 (28.6)	75	15
Impaired vision	1 (5.3)	18	0

* Results consistent with intrauterine rubella.

† Results not consistent with intrauterine rubella.

‡ Patients who had been immunised before study and in whom results were consistent with intrauterine rubella.

§ Rubella contact during pregnancy and supporting diagnosis made by a medical practitioner or laboratory testing.

|| Suspected rubella contact during pregnancy but no other complete supporting data and an absence of negating data.

* Mother reported rubella contact during pregnancy, and ophthalmological reports indicated retinal changes consistent with intrauterine rubella.

Forty eight of the 139 patients tested required Cendevax immunisation to clarify initial test results. None of these children failed to seroconvert after immunisation with Cendevax. One child had failed to seroconvert by six weeks according to both radial haemolysis and haemagglutination inhibition, but both methods showed seroconversion by 12 weeks after immunisation.

The table compares the clinical diagnoses with the results of the tests. The results showed a significant difference in incidence of positive test results between the patients with impaired hearing (29%) and those with impaired vision (5%) (Fisher's exact test; $p = 0.02$). Within the group of patients with impaired hearing the incidence of results consistent with intrauterine rubella was significantly higher in patients in whom intrauterine rubella was the "probable" cause of impaired hearing compared with the remainder of patients with impaired hearing (Fisher's exact test; $p = 0.0001$) or with the patients in whom rubella was "possibly" the cause of the deafness (Fisher's exact test; $p = 0.0006$).

Discussion

Intrauterine rubella may be diagnosed with certainty by: positive viral culture at or soon after birth; showing IgM anti-rubella antibodies in the neonatal period; or showing the presence of rubella antibodies persisting beyond the time at which maternal antibodies would have declined. If none of these tests is done in time diagnosis can be suggestive but never certain. The probability of rubella being the cause of deafness is higher

the more complete is the clinical syndrome. Nerve deafness alone, however, may be the only sign of intrauterine rubella, and it is unusual for this to be diagnosed clinically until the child is well past the age when viral cultures and antibody estimations are helpful.

The results of this study suggest that intrauterine rubella may be a much more common cause of deafness in childhood than is usually reported. In a survey in Australia of children born between 1949 and 1980 who had been fitted with hearing aids by the age of 18 years, maternal rubella during pregnancy was reported as the cause of deafness in 11.06% of cases.¹⁰ Maternal rubella was reported to be the aetiology of the deafness in 11 (10.8%) of the patients we tested (χ^2 test; NS). In 30 (28.6%) of our patients, however, laboratory results were consistent with their having had intrauterine rubella.

Examination of the incidence figures for Australia presented by Upfold and Isepy¹⁰ suggests that the true incidence may be considerably higher than 11.06%. Comparing the number of children with deafness due to rubella born in interepidemic (1961, 1962, 1969) and epidemic (1964, 1965, and 1966) years shows a total increase in deafness in 1964-6 of 536 cases, but only 312 of these were accounted for by intrauterine rubella. These figures suggest that only 58% of the cases truly due to intrauterine rubella are being diagnosed as such. A survey in the United Kingdom of the presence of rubella antibodies at the time of diagnosis of deafness suggested that rubella must account for at least 15% of all cases of sensorineural deafness.¹¹

In the group of patients in whom the clinical and laboratory results did not agree two children were investigated who had been diagnosed previously as having the congenital rubella syndrome on clinical grounds. Our initial test results did not confirm this diagnosis. One of these children had nerve deafness, a congenital heart lesion, and poor eyesight. On these grounds we classified her syndrome as being "probably" due to intrauterine rubella, but she had a normal rising antibody titre after immunisation. We noted that she had been investigated soon after birth and that serum was still available. This serum had the same IgG titre as maternal serum but had no IgM antibody. Thus despite the suggestive clinical syndrome this child's disease was almost certainly not due to intrauterine rubella. Another child who had many of the clinical signs of rubella (deafness, pulmonary stenosis, and retinopathy) on initial testing had antibody (58 IU) and a positive lymphocyte response in vitro (stimulation index = 6.8). Because of the strongly suggestive clinical picture the stimulation index was repeated. On this occasion the index was 3.2, a borderline result. This child's illness was almost certainly due to intrauterine rubella. The reason for the initially positive stimulation index was not clear.

A further five subjects gave false positive results—that is, an aetiology different from intrauterine rubella was volunteered by the parents but the tests suggested intrauterine rubella. In one case the aetiology of deafness was unknown but probably was not intrauterine rubella infection. Of the remaining four, two had Usher's syndrome, one the fetal warfarin syndrome, and one Down's syndrome. The two cases of Usher's syndrome were the only ones encountered in the study. These patients were not related, and neither child had a family history of Usher's syndrome. Further investigation of children with Usher's syndrome is planned.

In the study we did not encounter any children who failed to seroconvert after immunisation with Cendevax. The results of Cooper *et al*⁹ suggest that we may have underestimated the incidence of rubella because 10% of his patients with intrauterine rubella did seroconvert.

During the study two deaf patients were found who, despite showing high lymphocyte reactivity to in vitro stimulation with rubella antigen, lacked a rubella antibody titre by single radial haemolysis. Seronegativity was confirmed in one case by enzyme-linked immunosorbent assay, but in the other low positive specific IgG concentrations were found. These patients were not included in the table of results. At this stage, we can only suggest that this phenomenon might have been due to a

specific disorder in the production of rubella antibody or response to a cross reactive antigen at the lymphocyte level that was not reflected in antibody production. Another two women, investigated by us as part of a separate study, showed the same results despite repeated rubella vaccination. These cases suggest a specific disorder in the production of rubella antibody.

Apart from in the particular cases described, our test results compared well with the parents' concept of the aetiology of their child's hearing impairment. In the cases where the aetiology was unknown but rubella contact during pregnancy was reported testing showed that 26% of the children gave results consistent with intrauterine rubella.

In conclusion, the incidence of intrauterine rubella as a cause of deafness may be considerably higher than has been reported by obtaining a clinical history from parents. The incidence of rubella as a cause of visual impairment alone in a group of children and adolescents was significantly lower than that in the group of patients with impaired hearing.

We thank the children, parents, and controls who took part in the study; the director and staff of the National Acoustics Laboratories, Melbourne, the Audiology Department of the Royal Children's Hospital, the Visiting Teachers Service, Melbourne, the Low Vision Clinic, and the various schools for the deaf for helping us in contacting patients; Mr I Jack for the rubella antibody titres; and the Deafness Foundation, Victoria, for a financial grant.

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ONE HUNDRED YEARS AGO

In a recent report on the health of Penrith, Dr. J. D. Robertson records the result of a special investigation which he made into the circumstances attending a peculiar outbreak of diphtheria. The house in which the disease occurred was in every respect a most healthy residence, with large airy rooms, and the vicinity of the dwelling was quite free from any nuisance. The family were in comfortable circumstances, living in the most substantial manner as regards food. The only two possible causes for the appearance of the disease which presented themselves to Dr. Robertson were the water-supply (which contained a trace of sewage), and the influence of a fungous growth, which grew with the most extraordinary pertinacity and exuberance in the rooms more specially occupied by those affected. The defective spouting of the house was the cause of some damp at the windows and window-seats of the rooms referred to; and, from these situations, this fungus, of a fine hairy appearance, developed to an extraordinary extent, notwithstanding its repeated destruction. This growth also appeared on the arched roof of the milk-house, on which moisture collected and doubtless dropped into the milk, carrying with it this low form of growth. The association of diphtheria and low vegetable growths of this kind has been observed elsewhere, and the circumstance deserves record for future observation in connection with outbreaks of diphtheria. (*British Medical Journal* 1884;ii:1027.)