Prenatal diagnosis of congenital rubella

Rubella contracted in early pregnancy is associated with a high frequency of congenital anomalies in the infant. Viral transmission occurs in overt as well as occult maternal illness with or without a rise in maternal rubella antibody titres. It is thus both difficult and important to determine whether the fetus has become infected in utero. One approach is to isolate rubella virus from amniotic fluid, another immunoglobulin measurements. The development of sensitive haemagglutination inhibition (HI) tests has enabled us to establish normal levels for IgA, IgA₁, IgA₂, IgM, IgG, and IgD in amniotic fluid throughout gestation and investigate immunoglobulin levels in amniotic fluid as a diagnostic tool in detecting intrauterine infections.¹

Case report, methods, and results

An 18-year-old woman contracted clinical rubella during her eighth week of gestation with rising anti-rubella HI-titres. She underwent therapeutic abortion at 16 weeks of gestation by intra-amniotic installation of prostaglandin.

Specimen of amniotic fluid, fetal blood, and placenta were inoculated on to African green monkey kidney cell lines and incubated at 36°C for 10 days. The cell cultures were then challenged by Echo virus type II.² At 72 hours, no cytopathic effect was noted in specimens from the abortus and amniotic fluid. The non-cytopathic agent interfering with the growth of Echo virus was identified as rubella virus using BHK-21 clone 13 cell cultures and antisera to rubella virus.

IgA, its subgroups IgA₁ and IgA₂, IgM and IgD were measured semi-quantitatively by HI tests, where sheep red cells were coated with IgA₁, IgA₂, IgM, and IgD myeloma protein and specific rabbit antisera were used.¹ The sensitivity was 5 mg/l for IgA, 0.3 mg/l for IgM and 0.2 mg/l for IgD. IgG was determined on commercial radial immunodiffusion plates. Levels of the different immunoglobulins are listed in the table.

Second trimester immunoglobulin levels in amniotic fluid in (mg/l) in a case of congenital rubella and in 15 normal controls ± 1 standard deviation. IgM was not detected in 1 control. All other immunoglobulins were detected in all controls

IgA	IgA ₁	IgA ₂	IgD	IgG	IgM
<i>Congenital rubella</i>					
40	21	20	9	360	3
<i>Normal controls</i>					
30 $\pm$ 11	17 $\pm$ 6	12 $\pm$ 10	13 $\pm$ 9	500 $\pm$ 180	6 $\pm$ 10

Rubella HI assay was performed in duplicates of amniotic fluids and maternal serum using a standard microtechnique.³ The titre was 1/40 for maternal serum but negative for amniotic fluid.

Discussion

In contrast to previous reports⁴ we found IgM in amniotic fluid from 14/15 normal controls. The infected patient had normal concentration of IgM in amniotic fluid. IgA and its subgroups, IgA₁ and IgA₂, were present within the same range as reported⁵ in both the infected patient and the normal controls. This is an equally important finding, as IgA found in amniotic fluid has been proved to be of fetal origin using genetic markers⁶ and as the fetus can respond to intra-uterine infection with raised concentrations of IgA, IgM, both, or neither.¹ Although IgM was recovered in amniotic fluid, the anti-rubella titre was nil. This indicates that, though the fetus could produce IgM in normal amounts, it could not make rubella-specific antibodies. The lack of evidence of an immune response by this 16-week-old fetus may be attributed to either immune paralysis or inability of the fetus to produce this specific immune response during weeks 8-16 of gestation. This finding is consistent with the known ability of the rubella virus to persist in the fetus throughout gestation and early neonatal period.

It may be concluded that in the present case of congenital rubella, where rubella virus was recovered from the amniotic fluid and fetal tissues, determination of IgA, IgM, and IgD was not informative, although methods sensitive enough to detect these immunoglobulins in almost all normal controls were used. This confirms reports that

isolation of rubella virus from amniotic fluid is the only certain evidence of fetal infection at this time.

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Cornell University Medical College, New York, New York 10021, USA

LARS L CEDERQVIST, MD, assistant professor of obstetrics and gynaecology

IOANNIS A ZERVOUDAKIS, MD, assistant professor of obstetrics and gynaecology

LINDA C EWOL, BS, research technician in obstetrics and gynaecology

LAWRENCE B SENTERFIT, SCD, associate professor of microbiology

STEPHEN D LITWIN, MD, associate professor of medicine

Measles pneumonia in an adult

Primary viral pneumonia is a rare complication of measles. It occurs most frequently in immunodeficient children, in whom it is usually fatal. I report here a case of non-fatal measles pneumonia in a healthy adult.

Case report

A 28-year-old English woman presented with a four-day history of cough productive of yellow sputum with retrosternal soreness. She was febrile and had mild dyspnoea, malaise, and generalised itching. She had been treated symptomatically without antibiotics. There was no clear history of measles as a child. She was drowsy but orientated, dyspnoeic on exertion, but not cyanosed. Her temperature was 39.5°C, pulse 108, and she had a macular morbilliform rash on her face, neck, and upper back. There were a few white spots on her buccal mucosa. The physical signs in her chest were normal apart from coarse crepitations in the left middle and lower zones and right base. Haemoglobin was 11.8 g/dl, total leucocyte count $3.8 \times 10^9/l$ ($3800/mm^3$), 78% neutrophils, 20% lymphocytes. Chest x-ray examination showed patchy consolidation at the left base.

The patient was started on oral amoxycillin, 750 mg daily. The day after admission she became less well: her temperature was 40°C; she became centrally cyanosed; and the crepitations became more widespread. Chest radiography showed consolidation bilaterally. Her rash had spread over the entire chest and back, florid monilia was evident in the mouth (confirmed by a swab), and she also developed bilateral conjunctivitis. Her condition continued to deteriorate, with the development of widespread bronchial breathing, and oral flucloxacillin, 1 g daily, was added. Three days after admission she became confused and disorientated and arterial partial pressure of oxygen (Pao₂) while receiving oxygen at 5 l/min from an MC mask was 7.73 kPa (58 mm Hg), falling after 24 hours to 2.8 kPa (21 mm Hg). An x-ray film showed consolidation affecting both lungs in their entirety with bilateral air bronchograms. Haemoglobin was 11.5 g/dl; total leucocyte count $10 \times 10^9/l$, with 90% neutrophils and 8% lymphocytes.

She was intubated and ventilated with 10-cm positive end-expiratory pressure, and, as the diagnosis was still not clear, her treatment was changed to intravenous cloxacillin, 1 g daily; intravenous gentamicin, 240 mg daily; intramuscular oxytetracycline, 400 mg daily; and intravenous hydrocortisone, 800 mg in 24 hours tailing off over five days. Two hours after intubation Pao₂ was 8.93 kPa (67 mm Hg). Ventilation was continued for seven days, after which the patient slowly recovered, antibiotics being gradually discontinued. No organisms were isolated from the numerous specimens investigated apart from *Candida albicans* from sputum on admission and *Pseudomonas pyocyanea* from sputum while on the ventilator; this latter was thought to be a ventilator contaminant. The patient's serum was examined for antibodies to various viruses, rickettsiae, and the psittacosis agent as well as mycoplasmas. There was a rise in antibody to measles virus by complement fixation test, which rose from a titre of less than 1/8 on admission to 1/128 on day 17 and 1/256 on day 24. Studies of immunological competence were normal, apart from a lack of response to inactivated influenza virus vaccine.

Discussion

Measles giant-cell pneumonia has mainly been described in children with immunological deficiencies,^{1,2} although a paper describing Kenyan children with measles and pneumonia concluded that most cases of pneumonia were viral.³ In adults two cases of measles pneumonia have been reported, both fatal. One patient had a malignant reticulosis,⁴ and the other, also a 28-year-old woman, had an unclassified blood dyscrasia since childhood.⁵

The case I describe had no significant past history or gross immunological deficiency. Giant-cell measles pneumonia is a histological diagnosis not usually made during life, but the clinical picture, specific rise in antibody titre, and lack of bacterial growth lead us to consider this such a case.

I thank Dr J F Dow for permission to report on a patient under his care, and Dr J C Batten, Dr M J Boyd, and Dr J G Collier for their help and advice. Virological investigations were undertaken by Professor H Stern.

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Department of Medicine, St George's Hospital, London SW1

J J FASLER, BSC, MB, house officer (present address: Royal Victoria Hospital, Bournemouth, Dorset)

Delayed healing of varicose ulcer with levamisole

Levamisole (L-tetramisole), an anthelmintic drug, has been reported to restore delayed hypersensitivity reaction in patients with cancer.¹ The possible role of cell-mediated immunity in the pathogenesis of rheumatoid arthritis has been summarised by Yu and Peter.² Huskisson *et al*³ and Veys *et al*⁴ reported encouraging results of levamisole in patients with rheumatoid arthritis, whereas Dinai and Pras⁵ found no improvement and in some patients the arthritis even became worse. We have recently studied the effect of levamisole in rheumatoid arthritis. In one patient a healed varicose ulcer broke down and healed only with withdrawal of the drug. Since this possible complication has not apparently been reported we thought that it would be of interest.

Case history

A 67-year-old woman was seen first in May 1975 with a six-month history of polyarthritis. She had had morning stiffness and enlargement of several joints. She had been treated with salicylate, phenylbutazone, indomethacin, naproxen, ibuprofen, and more recently benorylate. Ten years earlier her varicose veins had been surgically stripped, and she had had a recent varicose ulcer which had completely healed. The results of laboratory tests included haemoglobin 9.5 g/dl, erythrocyte sedimentation rate 88 mm in first hour, and rheumatoid factor strongly positive at a titre of 1/2048. X-ray films of joints showed erosive changes typical of rheumatoid arthritis in many joints. The final factor of relevance was a history of penicillin allergy.

Treatment was begun in September 1975 with levamisole 50 mg, three times daily. One month later the patient complained of headache, dizziness, and vomiting, which she attributed to levamisole. She had also noticed that the healed varicose ulcer had started to break down. In December 1975 her arthritis had improved but the ulcer remained broken. Zinc sulphate, 660 mg daily, was begun. In February 1976 the patient developed purpuric rash on both forearms which disappeared after two weeks when levamisole medication was given on only two days each week. Nevertheless, the ulcer deteriorated and became larger and septic despite antibiotic ointment and Viscopaste dressings.

In June 1976 the patient developed mouth ulcers. The varicose ulcer reached 6 cm in diameter and had an irregular margin and purulent dis-

charge, while satellite ulcers appeared round its edge. Levamisole was stopped; the ulcer healed completely in one month; and the mouth ulcers, headache, and anorexia disappeared.

Discussion

Rash, fever, anorexia, nausea, giddiness, mouth ulcers, granulocytopenia, tremor, disturbance of taste, neurosensory irritability, and transient gastralgia have been the side effects of levamisole reported so far.³⁻⁵ In our patient treatment with levamisole was accompanied by the breakdown of a previously healed gravitational ulcer which promptly healed when the drug was discontinued. It is extremely difficult to be certain whether or not levamisole can be implicated as the cause of the breakdown of the ulcer, but it is surprising that not only did the ulcer continue to increase in size the longer the drug was prescribed, but satellite ulcers also appeared. The ulcer measured about 6 cm in diameter when levamisole was discontinued and had healed completely after only one month.

One would have to challenge the patient with a further course of levamisole to see whether the same events occurred to be certain of the causal relationship, but this we consider ethically unjustified. The post hoc, ergo propter hoc is a common fallacy in clinical medicine. Though we cannot prove this causal relationship, we know of no effect of levamisole on collagen turnover and wound healing other than its effect on cellular immunity.

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Centre for Rheumatic Diseases, University Department of Medicine, Royal Infirmary, Glasgow, Scotland

AHMED F EL-GHOBAREY, MRCP, research fellow

MYRON MAVRIKAKIS, MD, research fellow

IMOGEN MORGAN, MB, CHB, house officer

JEAN P MATHIEU, MD, Canadian Arthritis and Rheumatism Fellow

Retinitis pigmentosa and autoimmune endocrine abnormalities in identical twins

We report the concurrence of retinitis pigmentosa with autoimmune diseases in identical twin sisters, an association not previously described.

Case reports

Case 1—a 59-year-old woman, deaf and dumb since birth, was admitted to hospital with suspected gastroenteritis. She was found, however, to have hyperthyroidism; there were no ocular signs, but ophthalmoscopy showed retinitis pigmentosa.

The diagnosis of hyperthyroidism was confirmed biochemically, the serum thyroxine-iodine being 244 nmol/l (3.1 ng/ml) (normal range 60-140 nmol/l (1.1-8 ng/100 ml)) and the serum triiodothyronine 9 nmol/l (6 ng/ml) (normal range 1.25-3.75 nmol/l (0.8-2.4 ng/ml)). The 4-hour thyroid uptake of ¹³²I was increased at 83% and a thyroid scan showed a moderate goitre of the Graves's type. The serum cortisol concentrations before and after tetracosactrin stimulation were within the normal range and the resting plasma corticotrophin concentration was normal at 23 pg/l. The thyroglobulin red-cell agglutination titre was 1/25 000.

Immunofluorescence tests showed the presence of thyroid colloid and microsomal antibodies, and adrenocortical antibodies (twice, strongly positive) but gastric parietal cell, intrinsic factor, and mitochondrial and smooth muscle antibodies were not detected. Test results for rheumatoid and antinuclear factors were negative. The patient was given carbimazole