CASE REPORTS

Rubella polyneuropathy

I. W. TOMLINSON
M.B.B.S.

Combined Neurological Service, Hull Royal Infirmary, HU3 2JZ

Summary

Two cases of polyneuropathy occurring after rubella infections are described, together with the nerve biopsy and serological findings.

Introduction

Neurological complications of rubella infection are uncommon and usually take the form of encephalitis or encephalomyelitis (Humphreys and Ekermeyer, 1937; Margolis, Wilson and Top, 1943; Miller, 1956; Miller, Stanton and Gibbons, 1956; Steen and Torp, 1956; Sherman, Michaels and Kenny, 1965; Croft, 1969). Myelitis and polyneuropathies have also been described (Miller, Stanton and Gibbons, 1956; Pampiglione, Young and Ramsey, 1963) but are rare. In an exhaustive review of eighty cases of neurological complications following rubella infection, described in the literature up to 1956, Miller *et al.* (1956) could find only three reported cases of polyneuropathy, and since then we have been unable to find further cases reported in the literature. The purpose of this paper is to describe two cases of polyneuropathy following rubella infection, and to include the serological and nerve biopsy findings.

Case 1

A schoolboy, aged 15 years, was admitted to Pinderfields General Hospital, Wakefield. Five months before admission he had developed a typical rubella infection, and 3 days after the disappearance of the rash, noticed weakness in both legs and difficulty in walking. Two days after the development of weakness he was admitted to Leeds Road Hospital, Bradford. On admission, examination showed him to be apyrexial; cardiovascular, respiratory and gastrointestinal systems were normal, cranial nerves were normal, but he had moderate weakness of his lower limbs, complete areflexia, but no sensory deficit. Investigations, including full blood count, ESR, urine analysis and chest X-ray, were all normal. Virological studies were negative. The cerebrospinal fluid contained protein 27 mg/100 ml with two lymphocytes

on admission and, when retested 5 days later, contained protein 106 mg/100 ml and no cells. During the first week of his stay in hospital he developed dull aching pains in both calves and later both forearms. One week after admission he developed weakness of both arms, but no sensory signs developed at this time. He remained as an inpatient for 4 weeks, without obvious improvement, and was discharged with persisting weakness, but he was ambulant.

Three months later he was admitted to Pinderfields General Hospital, still complaining of weakness of all four limbs. At this time he was ambulant, but had difficulty standing on his toes and in turning. The cranial nerves were normal, but he had diffuse moderate weakness of the muscles of all four limbs, maximal distally with mild distal muscle wasting, and bilateral dropped feet. There was hypotonia of all four limbs and complete areflexia. He had a wide based stamping gait, and sensory ataxia of all four limbs. Investigations, including full blood count, ESR, urine analysis, blood urea and electrolytes, were all normal. Rubella haemagglutination inhibition antibody titre was 1 : 256, and rubella complement fixation antibody titre was 1 : 64.

He was treated with intensive physiotherapy and made a gradual but slow improvement; at the time of his discharge 3 weeks after admission, although he still had bilateral dropped feet he was able to walk without calipers, but still had trouble with his handwriting.

Case 2

A girl was born of unrelated parents. Following a normal pregnancy and delivery it was noted at birth that the infant had a congenital nystagmus, a dense left cataract and a convergent squint; the latter was corrected at the age of 3 years. At 6 years she sustained a head injury, without loss of consciousness, and without sequelae. Her general health had been good, apart from intermittent nocturnal enuresis.

She presented, at the age of 7 years 8 months, with a 5-week history of difficulty in doing up the buttons

on her clothes, and a 3-week history of deteriorating handwriting and unsteadiness on her feet. She had fallen frequently on this account. Two weeks before the onset of her symptoms she had been in contact with two children with rubella infection in her street at home.

On admission she was fully conscious, and examination showed a congenital nystagmus, a dense left cataract but otherwise normal cranial nerves. She had generalized hypotonia in all limbs, and weakness of the distal muscles of all four limbs, producing clawing of the fingers of both hands, and bilateral dropped feet. Tendon reflexes were reduced in both arms and absent in the legs, with flexor plantar responses. Sensory testing revealed a mild impairment of touch, pain and vibration sense in stocking distribution up to the knees.

Investigations, including radiographs of skull and chest, full blood count, ESR, blood sugar and urine analysis, were normal. The cerebrospinal fluid contained protein 40 mg/100 ml, with γ -globulin 7%, sugar 55 mg/100 ml, and no cells. The CSF protein remained normal at two subsequent examinations. Liver function tests and serum proteins were normal, as were urinary coproporphyrins and uroporphyrins, serum calcium and phosphate. Nerve conduction studies showed marked slowing of motor conduction, the velocity in the left ulnar nerve being 13 m/sec, and that in the right lateral popliteal nerve being 14 m/sec. A limited electromyographic study done shortly after admission was normal. The Paul-Bunnell Test and urine examination for metachromatic granules were negative. Virus tissue cultures of CSF, blood and faeces were negative; plasma immunoglobulin levels were normal. Serological testing for rubella antibodies, measured over 6 weeks are shown in Table 1. These levels are compatible with a recent rubella infection. Nerve and muscle biopsy were performed.

TABLE 1. Case 2. Serial rubella antibody titres in first 6 weeks of illness

	Complement fixation titres	Haemagglutination inhibition titres
Specimen 1	1 : 20	1 : 320
Specimen 2	1 : 20	1 : 640
Specimen 3	1 : 20	1 : 1280
Specimen 4	1 : 20	1 : 1280

Nerve biopsy (Dr D. G. F. Harriman)

Biopsy of the left musculo-cutaneous nerve of leg shows no overall loss of myelinated fibres; some separation of fascicles suggest oedema, and one or two epineural vessels are scantily cuffed by lymphocytes and histiocytes. Occasional fibres show myelin disintegration, and naked axons can be

found indicating segmental demyelination. There are clusters of fine axons, probably regenerating.

Muscle biopsy of left peroneus brevis shows no atrophy, but large numbers of target fibres (type 1) with the motor innervation showing limited sprouting with excessive beading of subterminal fibres are seen.

Conclusion

Polyneuritis; with no specific features.

The patient's condition gradually deteriorated, the limbs becoming progressively weaker and areflexic, and 5 weeks after admission, since she had become unable to walk, she was started on prednisone 20 mg t.d.s. A gradual improvement started in the next week and continued over the next month. She was discharged home, on prednisone 10 mg twice daily, able to write and walk without support. Power and sensation further improved under outpatient observation, and sensation returned to normal within 2 months of her discharge from hospital, during which time she attended school regularly.

Improvement in power continued on reduced doses of prednisone, and 5 months following her discharge from hospital the steroids were stopped completely by which time she was clinically well, sensation and power being normal.

Discussion

Acute encephalomyelitis complicating specific fevers and prophylactic inoculation is well recognized, but occurs far more commonly with measles, mumps and varicella than with rubella (McNairn Scott, 1967). The incidence of neurological complications following rubella has been estimated at between 1 in 5000 cases (Sherman *et al.*, 1965) and 1 in 6000 cases (Margolis *et al.*, 1943), though this is considered an underestimate by Pampiglione (Pampiglione *et al.*, 1963). However, polyradiculitis accounted for only 4% of the neurological complications following rubella, encountered by Miller *et al.* (1956) in their review of the literature.

Clinical diagnosis of the polyradiculopathy usually presents no difficulty as the rash of rubella generally precedes the onset of neurological symptoms by an average of 8-7 days (Miller *et al.*, 1956) but in the second case described above no rash was seen, although it may have been so mild as to have passed unnoticed. This could well be the case in other patients with polyneuropathies where no apparent cause is found, and in such cases we feel that rubella should always be considered as a possible cause.

Nerve biopsy in our second case showed only relatively non-specific pathological changes, resembling those described by McNairn Scott (1967), who concluded that only non-specific changes of

oedema, perivascular cuffing and microscopic haemorrhages were the rule, perivenous demyelination being exceptional. The precise mechanism of the production of the nerve damage is consequently far from settled. The various theories have been recently reviewed by Croft (1969): (1) that nerve damage is due to direct invasion of the nervous system by the virus; (2) that there is activation of some previously present quiescent virus harboured by the patient; (3) that the damage is due to some form of allergic reaction in the nervous system.

Direct invasion of the nervous system by the virus has recently been demonstrated in cases of measles encephalitis (Adams, Baird and Filloy, 1966) but it is doubtful whether this is the case in rubella infections.

The theory of activation of a latent virus previously present was proposed by Greenfield (1929) but no evidence of any such virus has been found.

The role of allergy in the production of nerve damage has been discussed at length by Koprowski (1962), who postulated that, as a mechanism, the antigenic material released following direct neural invasion by the virus might induce production of antibodies sharing antigenic determinants with neural tissue, or with released material from other damaged tissues.

More recently, Webb and Smith (1966) have advanced the theory of a biphasic mechanism: an initial viraemia followed by a phase of antigen-antibody reactions between persistent viruses within the neural tissue and circulating antibody, the reaction occurring predominantly at perivascular sites in the neural tissues, and producing the characteristic perivascular inflammation seen in biopsy material.

A previous study of rubella antibody levels in encephalopathies (Sherman *et al.*, 1965) produced no conclusive results. The first patient described above had raised titres of both rubella haemagglutination antibody (HIA) and rubella complement fixation (CF) antibody, indicative of recent rubella infection. In the second case, the very high HIA titre, 1 : 1280, would make a diagnosis of congenital rubella highly unlikely, despite the presence of congenital nystagmus and cataract. In congenital rubella infections the HIA levels decline more rapidly than in acquired rubella (Kendrick *et al.*, 1968), so that after 5 years the mean HIA titres in congenital rubella are 1 : 14, compared with a mean titre of 1 : 63 in patients with acquired rubella (Cooper *et al.*, 1971). Our patient's titre of 1 : 1280 therefore indicates recent infection.

Prognosis and treatment

Of the three cases of polyradiculopathy reviewed by Miller *et al.*, in 1956, complete recovery occurred in two, in 8 and 10 weeks respectively, without drug

therapy. In our first case, recovery without drug therapy was only partial after 20 weeks; but in our second case the patient had made a satisfactory recovery at the time of discharge, 9 weeks after admission; she was treated with prednisone, and continued to improve on reduced doses of the drug following discharge from hospital. The place of steroids in the management of the post-infective polyneuropathies is not settled but we feel they are of value in cases where respiration is threatened, in cases not spontaneously improving, and in those who are deteriorating under observation.

Acknowledgment

I am indebted to Dr John Pearce for permission to publish these cases and for help in preparing the manuscript.

References

- ADAMS, J.M., BAIRD, C. & FILLOY, L. (1966) Inclusion bodies in measles encephalitis. *Journal of the American Medical Association*, **196**, 290.
- COOPER, L.Z., FLORMAN, A.L., ZIRING, P.R. & KRUGMAN, S. (1971) Loss of rubella haemagglutination inhibition antibody in congenital rubella. *American Journal of Diseases of Children*, **122**, 397.
- CROFT, P.B. (1969) Para-infectious and post-vaccinal encephalomyelitis. *Postgraduate Medical Journal*, **45**, 392.
- GREENFIELD, J.G. (1929) The pathology of measles encephalomyelitis. *Brain*, **52**, 171.
- HUMPHREYS, T.F. & EKERMEYER, E.W. (1937) Rubella: Report on an epidemic with an unusual number of complications and relapses. *Ohio State Medical Journal*, **33**, 406.
- KENDRICK, K.G., SLINN, R.F., DORMAN, D.C. & MENSER, M.A. (1968) Immunoglobulins and rubella virus antibodies in adults with congenital rubella. *Lancet*, **i**, 548.
- KOPROWSKI, L. (1962) The role of hyperergy in measles encephalitis. *American Journal of Diseases of Children*, **103**, 273.
- MARGOLIS, F.W., WILSON, J.L. & TOP, F.H. (1943) Post-rubella encephalomyelitis—Report of cases in Detroit and review of literature. *Journal of Pediatrics*, **23**, 158.
- MCLAIRN SCOTT, T. (1967) Post-infectious and vaccinal encephalitis. *Medical Clinics of North America*, **51**, 701.
- MILLER, H.G. (1956) Discussion on the neurological complications of the specific fevers. *Proceedings of the Royal Society of Medicine*, **49**, 139.
- MILLER, H.G., STANTON, J.B. & GIBBONS, J.L. (1956) Para-infectious encephalomyelitis and related syndromes. Critical review of neurological complications of certain specific fevers. *Quarterly Journal of Medicine*, **25**, 427.
- PAMPIGLIONE, G., YOUNG, S.E. & RAMSEY, A.M. (1963) Neurological and electroencephalographic problems of the rubella epidemic of 1962. *British Medical Journal*, **ii**, 1300.
- SHERMAN, F.E., MICHAELS, R.H. & KENNY, F.M. (1965) Acute encephalopathy (encephalitis) complicating rubella. Report of cases with virological studies, cortisol-production determinations and observations at autopsy. *Journal of the American Medical Association*, **192**, 675.
- STEEN, E. & TORP, K.H. (1956) Encephalitis and thrombocytopenic purpura after rubella. *Archives of Diseases in Childhood*, **31**, 470.
- WEBB, H.E. & SMITH, C.E.G. (1966) Relation of immune response to development of central nervous system lesions in virus infection in man. *British Medical Journal*, **ii**, 1179.