stances to a patient whose leucocyte count is below 8,000 per c.mm. or to one who manifests purpura or a sharp fall in platelet level.

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RUBELLA ENCEPHALITIS

BY

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Since the classical description by Bénard (1921) of 13 cases of encephalitis occurring amongst 291 hospital patients with rubella, there has been considerable interest in this and other not uncommon complications of the latter. Steen and Torp (1956) reported 88 definite cases of rubella encephalitis from the literature, and added a further three cases of their own. Most of the reported cases have occurred during epidemics of rubella.

The neurological symptoms most often occur one to six days after the onset of the exanthem. They are characteristically brief in duration, with complete recovery in most cases. Usually encephalitic, myelitic, or meningitic signs are elicited either singly or in combination. Death can occur (it occurred in 20% of the cases reviewed by Schleisner *et al.*, 1955). More rarely, permanent sequelae are encountered.

Cases of rubella complicated by neurological involvement do not seem to differ in any way from cases not so affected. Further, there is no relationship between the severity of the initial illness and the occurrence of neurological complications (Barraclough, 1937).

Case 1

A girl aged 6 years was admitted to hospital during a mild epidemic of rubella with a history of onset of headache and drowsiness seven days previously. Next day she developed a generalized maculopapular rash diagnosed by the family physician as rubella. A younger sister aged 3 had developed rubella one week previously, and, although drowsy at the time of the rash, rapidly recovered as the rash faded.

As the exanthem subsided, the patient's drowsiness increased, and the persistence of this together with the severe headache resulted in her being confined to bed. Three days before admission she noticed the gradual onset of "giddiness," which became worse whenever she attempted to sit up in bed. This in turn became progressively worse, until on the day of admission vomiting occurred whenever the "giddiness" was severe. There had been no convulsions or loss

of consciousness, and no diplopia, speech disturbance, or dysphagia. The child had previously suffered from measles, mumps, chicken-pox, and infantile eczema.

Neurological examination revealed an afebrile, intelligent, co-operative girl who continually lapsed into a drowsy state when not engaged in conversation. There was no evidence of cranial nerve involvement and ophthalmoscopic examination was normal. Abnormal findings included mild bilateral horizontal nystagmus and intention tremor. The tendon reflexes were all brisk, but the plantar responses were flexor. Kernig's sign was negative. She had gross ataxia with vertigo when erect, the ataxia being most pronounced when the eyes were closed. There was a tendency to walk on a wide base. The only other positive finding on examination was pharyngitis with fetor. A provisional diagnosis of rubella encephalitis was made and symptomatic treatment given.

Investigations.—Mantoux reaction 1:1,000 negative. Throat swab—no pathogens. X-ray examination of skull and chest normal. E.S.R., 32 mm. in one hour. Lumbar puncture on admission: clear colourless fluid; pressure 70 mm. water; cells, less than one leucocyte/c.mm.; chloride, 125 mEq/litre; protein, 20 mg./100 ml.; Pandey reaction negative; W.R. negative; glucose, 29 mg./100 ml. (probably unreliable, as the specimen was left in the refrigerator overnight without preservative); Hb, 12.7 g./100 ml.; W.B.C., 10,000/c.mm. (55% neutrophils, 40% lymphocytes, 5% monocytes).

Four days after admission the E.S.R. was 16 mm. in one hour; W.B.C., 6,000/c.mm. (30% neutrophils, 60% lymphocytes, 5% monocytes, 5% eosinophils). Lumbar puncture 11 days after admission: cells, 3 leucocytes/c.mm.; chlorides, 117 mEq/l.; glucose, 60 mg./100 ml.; protein, 60 mg./100 ml.; Pandey reaction negative.

The drowsiness and vomiting continued for a further three days, but the vertigo and ataxia lasted another day. From this time onward, recovery was rapid and the patient was discharged 15 days after admission with no residual disability. Two weeks later she started at school again, having made an apparently full recovery.

Case 2

A girl aged 8½ years, the youngest of three children, was admitted to hospital with a history that seven days previously she had had fever and rash. The rash, which faded in two days, was diagnosed by the family physician as rubella. She was well in herself at the time and remained so until the morning of the day of admission, when she awoke with headache and anorexia, and was "off colour" all day. That evening she vomited and had a generalized convulsion which lasted 1½ hours and left her stuporous. She had previously had measles and whooping-cough, but no convulsions.

The mother and two other children were well. The father had had a temporary "influenza"-like illness with fever, headache, sweating, and generalized muscular pains one week before.

On neurological examination the temperature was 99.6° F. (37.6° C.) and pulse 36. The patient was semiconscious, very restless and uncooperative, and showed no recognition of her surroundings. The pupils were equal and reacted to light. Cranial nerve palsies were not present. There was moderate nuchal rigidity, with a positive Kernig's sign. Tendon reflexes were all present but brisk, the plantar responses uncertain. The only other positive finding was an inflamed throat. Her weight was 70% of normal for her age. A diagnosis of rubella meningo-encephalitis was made and she was kept sedated with intramuscular phenobarbitone.

By next morning she was fully conscious but still rather drowsy. She was not confused but had some retrograde amnesia. She was now afebrile and had had no further convulsions. She remained well subsequently and was discharged one week after admission, having phenobarbitone ½ gr. (32 mg.) b.d. When seen three weeks later she was very well and the phenobarbitone was discontinued.

She attended the out-patient department 2½ years later for another complaint, and showed no sequelae of the meningo-encephalitis. Her weight at this time, however, was normal for her age. There was no thirst, polyuria, or somnolence, and the moderate obesity present was thought to be nutritional in origin.

Discussion

As with the encephalitis occasionally associated with other exanthemata, the mode of production of rubella encephalitis is obscure. Three possibilities can be considered: (1) that the encephalitis is due to the rubella virus itself; (2) that the encephalitis is due to the activation of a previously latent encephalotropic virus; and (3) that the encephalitis is the result of an antigen-antibody reaction. All these possibilities are discussed at length by Davison and Friedfeld (1938) and Hurst (1952), and are not considered further here.

The incidence is not known with certainty, as rubella is not notifiable, and many of the milder cases are not reported. However, rubella encephalitis is probably more frequent than the literature suggests, as most neurologists and paediatricians have seen at least one such case. Shaw (1952) showed that the incidence of encephalitis complicating morbilli was 1 in 616, whilst Greenberg *et al.* (1955) reported an incidence of 1 in 702 in New York City. Comparable figures for rubella encephalitis have been obtained during epidemics in closed communities (see Table). Humphrey

Comparative Incidence of Rubella Encephalitis

	Incidence	Mortality Rate	Permanent Sequelae
Morbilli encephalitis	1: 1,000 (Litvak, <i>et al.</i> , 1943) 1: 616 (Shaw, 1952) 1: 702 (Greenberg <i>et al.</i> , 1955)	20% (Hamilton and Hanna, 1941) 23.8% (Steen, 1954) 10% (McMath, 1954) 2.7% (Knouf and Bower, 1954)	40% (Hamilton and Hanna, 1941) 45% (30% serious) (Steen, 1954)
Rubella encephalitis	1: 305 (Humphrey and Ekermeier, 1937) 1: 640 (Margolis <i>et al.</i> , 1943)	20% (Schleisner <i>et al.</i> , 1955)	Very rare. (No figures available)
Vaccinia encephalitis	1: 170,000 (Weinstein, 1947) 1: 110,000 (Greenberg and Appelbaum, 1948) 1: 100,000 (Conybeare, 1948)	9% (Greenberg and Appelbaum, 1948) 51% (Herrlich, <i>et al.</i> , 1956)	28% (Herrlich <i>et al.</i> , 1956)
Varicella encephalitis		11% (Underwood, 1935) 11% (Conybeare, 1956)	15% (Underwood, 1935) 10% (Ford, 1952)
Mumps encephalitis	1: 4-1: 5 (Bowers and Weatherhead, 1953) (varies from epidemic to epidemic)	Only 15 in literature (Steiner, 1942) 3-6% (Conybeare, 1956)	20% (Oldfeldt, 1949) 2.5% (Bowers and Weatherhead, 1953)

and Ekermeier (1937) described one case of encephalitis occurring amongst 305 cases of rubella during an epidemic in a children's home in 1935. In the Detroit epidemic reported by Margolis *et al.* (1943) 14 of the 9,000 cases of rubella were complicated by encephalitis—an incidence of 1 in 640.

These figures differ little from those found by Shaw in morbilli encephalitis. Thus earlier views that rubella is complicated by encephalitis less frequently than is morbilli are not justified.

The majority of cases occur during childhood, but this is probably due to the fact that rubella is more frequent in childhood. Margolis *et al.* (1943) reviewed 40 cases from the literature in which the ages were known—25 were under the age of 13. The sex incidence is equal.

Clinical Patterns

Owing to the variability and widespread nature of the neurological lesions, a multiplicity of signs and symptoms

may be encountered. Generally speaking, as in all encephalopathies occurring with the exanthemata, there are three main clinical patterns:

1. *Meningo-encephalitis*.—In this group the main features are headache, drowsiness, and vomiting, with a positive Kernig sign and brisk tendon-jerks. Some cases have a moderate fever.

2. *Encephalitis*.—In this group the main features are confusion, drowsiness which may go on to coma, delirium, convulsions, and cranial nerve palsies. If the cerebellum is involved, vertigo, ataxia, and nystagmus may be prominent (Case 1). When cerebellar signs predominate the prognosis is very good. Occasionally the extrapyramidal system is involved, with tremor and involuntary movements (Goldbloom and Keith, 1937).

3. *Encephalomyelitis*.—In this group, in addition to the above manifestations, evidence of cord involvement with sphincter disturbances (usually urinary retention), and dorsal column and pyramidal tract signs as well, will be encountered.

In the U.K. rubella epidemic which occurred in 1940, polyneuritis was also described as a neurological complication of rubella (Harrison, 1940; Hodges, 1940; Sprott, 1940). Owen and Greenaway (1940) also described a case of rubella which was complicated by retrobulbar neuritis.

Neurological symptoms usually occur after the appearance of the exanthem. This interval varies between one and six days. C.N.S. complications, however, may on rare occasions precede the rash by two to nine days (Zadik, 1927; de Gennes *et al.*, 1934; Rodriguez *et al.*, 1947; Holliday, 1950; Mitchell and Pampiglione, 1954; Steen and Torp, 1956). Bradford (1943) reported a case of rubella encephalomyelitis in which the rash recurred 12 days after the onset of neurological symptoms. Recurrence of the rash, however, is not a rare phenomenon. Humphrey and Ekermeier (1937), studying an outbreak of rubella in a children's home, found that 6% of the children had second attacks of rubella at periods varying from 12 to 43 days after the onset of the initial attack.

The cerebrospinal fluid is usually clear and under normal pressure. There may be a lymphocytic pleocytosis, and the protein, although often normal at the onset, may be raised later. The glucose content is normal.

An initial leucopenia occurs during the exanthematous stage, but a leucocytosis in which neutrophils predominate occurs during the encephalitic phase.

Diagnosis, Prognosis, and Treatment

As Borch Jørgensen (1955) has pointed out, in all cases there is a disordered state of consciousness varying from mild drowsiness to deep coma. This, together with the recent history of rubella and the neutrophil leucocytosis, gives the clue to the diagnosis. The C.S.F. should be examined in all suspected cases to exclude purulent meningitis.

There are no outstanding differences between the pathological changes encountered in rubella encephalitis and the encephalitis which may complicate the other acute exanthemata. Microscopically there is oedema of the brain, and congestion of the meninges when they are affected. Microscopically, the white matter bears the brunt of the damage (McNair Scott, 1952). Generalized hyperaemia with ganglion-cell degeneration and perivascular infiltration with lymphocytes, plasma cells, and microglia, have been described. In contrast to morbilli encephalitis, no pronounced demyelination has been recorded (Ford, 1952).

Neurological complications of rubella are usually acute and self-limiting, often within a few days. Death does occur, however (see Table). Of the cases of rubella encephalitis described in the literature, Schleisner *et al.* (1955) noted a mortality rate of 20%. In these cases death usually occurred within a few days of the onset of the encephalitis, and in many cases was preceded by hyperpyrexia (Schleisner *et al.*, 1955). Bulbar palsy was not infrequently a terminal event.

There are few recorded cases of permanent sequelae following rubella encephalitis. These have included ataxia, cranial nerve palsies, and personality changes (Davison and Friedfeld, 1938; Vestergaard, 1949). In the case described by Mitchell and Pampiglione (1954), despite severe neurological signs and gross mental changes at the height of the encephalitis, follow-up at six months revealed no sequelae and the intelligence was unaffected. The Table compares the incidence, mortality rate, and sequelae of the encephalitis that may follow morbilli, rubella, varicella, mumps, and vaccination with vaccinia virus.

No specific therapy is available, and the patient should receive symptomatic treatment: convulsions should be controlled by barbiturates, feeding given by an indwelling polyethylene tube in the comatose patient, and antibiotics given to control secondary bacterial infection.

Kabat *et al.* (1952) studied the effect of cortisone on acute disseminated encephalomyelitis produced experimentally in rhesus monkeys. They found that the steroids had a capacity to inhibit granuloma formation, a condition which is essential for the production of the encephalomyelitis. The modification of the granulomatous response in turn leads to antibody suppression. From these results, and from the fact that rubella encephalitis may well be a consequence of an antigen-antibody reaction, it would seem reasonable to use the steroids in the treatment of rubella encephalitis. Schleisner *et al.* (1955) treated two cases that developed hyperpyrexia (usually a terminal phenomenon) with cortisone and chlorpromazine. There was a dramatic subsidence of the fever, with complete recovery in both cases.

Summary

A case of rubella encephalitis with predominant cerebellar signs is described, the onset of which preceded the eruption by one day. Another case of rubella meningo-encephalitis is described, the onset of which followed the eruption by one week.

In each instance full recovery ensued and there have been no sequelae. The aetiology, incidence, clinical patterns, pathology, prognosis, sequelae, and treatment of the neurological lesions complicating rubella are discussed. Contrary to general opinion, there is evidence to suggest that the incidence of rubella encephalitis (unlike its sequelae) differs little from that of morbilli encephalitis.

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FURTHER OBSERVATIONS ON LONDON FOG

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In an earlier paper (Waller and Lawther, 1955) we reported some observations on fog in London during the winter of 1954-5. In particular, it was noted that a brief period of smoke "fog" in January appeared to affect adversely some patients with chronic bronchitis and emphysema. No water droplets were present at that time, and sulphuric acid was not detected by the methods used. It was, however, pointed out that traces of acid might have been present in the form of minute droplets. During the following winter the Department of Scientific and Industrial Research organized more detailed "smog" measurements in London and some other large towns, using Civil Defence volunteers as observers, and the opportunity was taken to extend the clinical study of patients with chronic bronchitis and emphysema to areas likely to be covered by the measurements.

The D.S.I.R. scheme was used during a dense and persistent fog which occurred early in January, 1956, and the measurements showed that "the distribution of the pollutants was very uneven, wide differences being noted in the concentrations observed from hour to hour at any place and from street to street at any time" (D.S.I.R., 1957). The tests were instantaneous and showed concentrations of smoke and sulphur dioxide 20 or more times the normal. Even greater increases were observed in the sulphate content of the air, and this could have been due to the presence of sulphuric acid. Though these data provided useful information about pollution on one or two notable occasions during the winter, it has proved more convenient to use for the clinical studies the results obtained with routine daily instruments. The present paper deals only with the Greater London group of patients; results from provincial centres will be included in a later paper.

Clinical Observations

As in the work reported earlier, patients with an established diagnosis of chronic bronchitis and emphysema attending a special clinic at this hospital were given diaries in which to record daily their own assessment of their health by means of a simple code.

The five centres taking part were St. Bartholomew's Hospital, Hammersmith Hospital, and the Chest Clinics at East Ham, Croydon, and Edgware. As the areas of residence