NEUROLOGICAL AND ELECTROENCEPHALOGRAPHIC PROBLEMS OF THE RUBELLA EPIDEMIC OF 1962

BY

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The epidemic of rubella in 1962 afforded an opportunity to study not only the common features and course of the illness but also a number of somewhat unusual complications.

Involvement of the central nervous system in rubella has been regarded as a rare occurrence. The early literature reviewed by Kinnier Wilson (1940) was supplemented among others by Margolis *et al.* (1943), Mitchell and Pampiglione (1954), Radermecker (1956), and by the extensive survey of Miller *et al.* (1956), who mention that out of 80 cases from the literature the average time of onset of encephalitis was four days after the appearance of the rubella rash. In six cases, however, the neurological illness began before the appearance of the rash. In fatal cases death occurred in three days, and the overall mortality was fairly high. The occurrence of coma and convulsions was thought to be an unfavourable sign. Changes in the cerebrospinal fluid were found to be of little prognostic significance. Reports of electroencephalographic studies either in complicated or uncomplicated cases of rubella are few (Mitchell and Pampiglione, 1954; Gibbs *et al.*, 1959).

In another paper (Young and Ramsay, 1963) the clinical aspects and the differential diagnosis of this usually mild disease are discussed. In the present study particular attention was devoted to the examination of the central nervous system, both during the initial phases of rubella and subsequently. Rubella as we know it clinically has a number of manifestations common to various disease entities. Only carefully timed laboratory studies in each individual patient can help to determine the nature of the aetiological factors. The isolation of a rubella virus had not been achieved in the U.K. early in 1962, and for practical clinical purposes we had to postulate that during the 1962 epidemic we were dealing with a single aetiological agent.

Most of the patients during that epidemic made an uneventful recovery, and those with uncomplicated rubella who were admitted to hospital (largely for social reasons) were discharged on the sixth or seventh day of illness. No definite cases of arthritis were seen in some 70 patients under the care of one of us (A. M. R.), although six adults complained of transitory pain in various joints. In the same group, one patient developed mild myocarditis. Respiratory insufficiency requiring assisted respiration occurred in one patient only.

Present Investigation

In the present study, planned to detect any involvement of the central nervous system in this usually mild disease, a scheme of daily observations was adopted. In addition to the usual clinical examination, the occurrence was noted of headache, irritability, drowsiness, photophobia and visual disturbances, nausea or vomiting, neck stiffness, pain or abnormal sensations in the body or limbs, minor involuntary movements, as well as more obvious features such as stupor, coma, convulsions, confusional states, speech and motor disorders.

In view of the work of Gibbs *et al.* (1959) it was agreed to study the E.E.G. patterns in patients with rubella, whether with or without complications. However, on account of the limited facilities at the peak of the epidemic priority for E.E.G. studies in the initial and later phases of rubella was given to patients with neurological complications. Altogether 23 patients had systematic E.E.G. studies in the course of their illness. With the use of a mobile neurophysiological unit with portable E.E.G. apparatus, records were taken on selected patients at the South Middlesex Hospital, St. Ann's General Hospital, and the Hospital for Sick Children, Great Ormond Street, in addition to the main bulk of patients seen at the Infectious Diseases Department of the Royal Free Hospital.

Severe clinical complications with a period of coma for one or more days, followed by stupor or gross confusion, were seen in three patients. Convulsions were reported in two of them, as well as in two other patients who did not remain unconscious for more than a few minutes. Drowsiness was noticed in eight patients, including the four who had convulsions. The significance of headache was difficult to evaluate; while generally a feature of the prodromal phase of rubella, it was not a prominent feature in the course of the illness, prior to or at the time of the neurological complications. Vomiting was uncommon, occurring in only two patients, in neither of whom was it severe. Neck stiffness, involuntary movements of the limbs, and irritability occurred only in patients with other gross neurological complications. Vague pains, mainly associated with joints, occurred in some adults, without evidence of local inflammation. Only one patient complained of severe pain and paraesthesiae.

The following case reports illustrate some of the problems in the interpretation of neurological and E.E.G. features during the 1962 epidemic of rubella.

Case Reports

Case 1.—A boy aged 6, who had no history of previous severe illness, developed on April 16, 1962, a rubella rash which lasted for three days. On April 18 he complained of headache and began to vomit. On April 21 two generalized convulsions occurred; he became semicomatose and was admitted to hospital. The cerebrospinal fluid contained 180 W.B.C. (all lymphocytes) and 100 mg. of protein per 100 ml. A severe E.E.G. abnormality was noted on the same day, while the patient was still semiconscious (Fig. 1). A total of 130 mg. of prednisolone was given over a period of eight days and the child recovered in two days. Considerable improvement was seen in the E.E.G. taken on May 11. Clinically the child made a complete recovery, while the E.E.G. remained mildly abnormal on subsequent examinations (June 28, July 31, and November 13).

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Case 2.—A girl aged 13, a rubella contact, developed a rash lasting for one day on April 2, 1962, and complained of pain and paraesthesiae in the legs, and a feeling of weakness three days later, followed by urinary retention. Thereafter she was confused for about four days. Motor and sensory impairment ascending to the level of the sixth cervical segment occurred, with bilateral optic neuritis and a right facial weakness. The cerebrospinal fluid (C.S.F.) contained 746 cells (78% polymorphs) and 550 mg. of protein per 100 ml. Assisted ventilation was necessary from April 10 for 20 days. A total dose of 860 mg. of prednisolone was given over a period of 22 days, starting on April 8. One year later recovery of function had occurred in her eyes, face, and arms, but she was walking with callipers and had a manually controlled bladder function. The E.E.G. taken on April 24 showed only a mild diffuse abnormality, suggesting that her brain had not been involved to the same extent as her spinal cord.

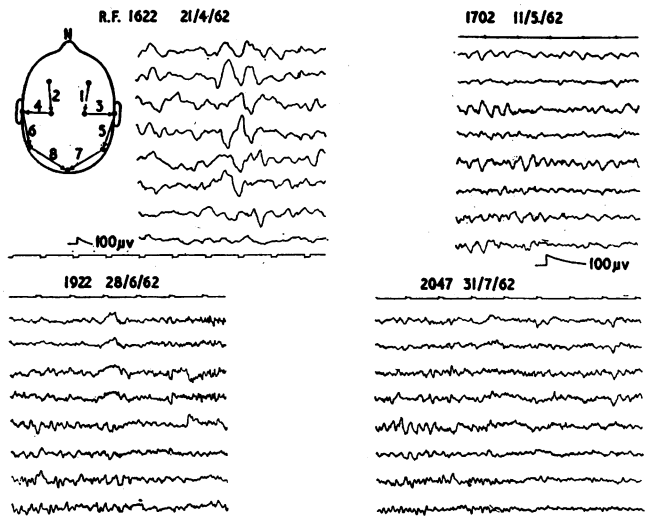

FIG. 1.—Case 1.

Case 3.—A girl aged 12, a rubella contact with no history of previous convulsions or severe illness, developed a rash on April 9, 1963, which faded three days later. High fever, coma, and convulsions occurred on April 14 and she was admitted to hospital. The C.S.F. contained 64 W.B.C. (75% polymorphs) and 125 mg. of protein per 100 ml. Prednisolone was started on April 16 and a total dose of 290 mg. was given over a period of 15 days. After the fifth day of unconsciousness she began to recover. On April 20 she was able to say a few words, and 10 days later was believed to have fully recovered.

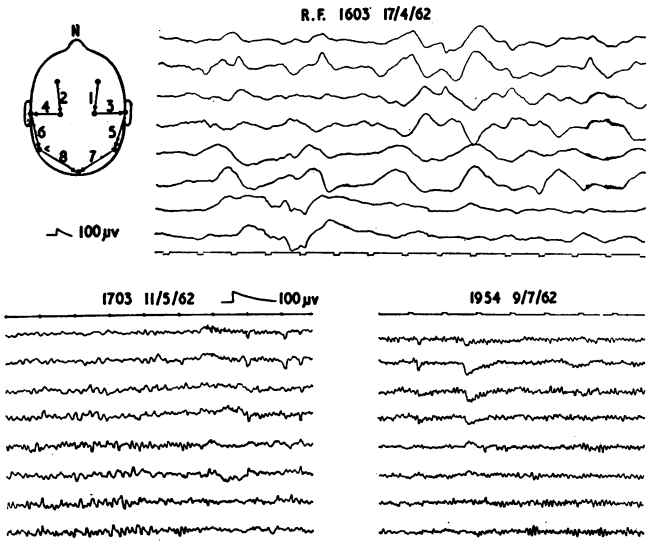

FIG. 2.—Case 3.

The first E.E.G. was taken on April 17 while she was still comatose (Fig. 2). A very severe generalized abnormality was seen, with large-amplitude very slow waves and a slight asymmetry between the activities of the two hemispheres. No discharges were observed. By April 21 the E.E.G. features had improved considerably and further amelioration occurred in subsequent months. Only a minimal residual E.E.G. abnormality, without focal or paroxysmal features, persisted on July 9 and October 8.

Case 4.—A girl aged 8, a sister of Case 3, developed a rubella rash nine days after her sister, on April 18. She was admitted to the same hospital on the next day, while her sister was still in coma. No complications occurred, and no gross abnormality was seen in the E.E.G.s of this child recorded on April 21 and 28 (Fig. 3). The E.E.G. studies were carried out at comparable time intervals to those of her sister, who probably had been affected by the same illness.

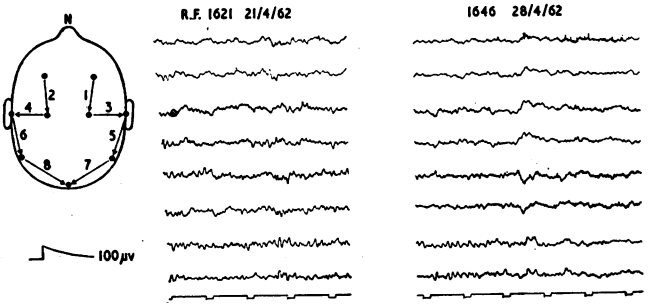

FIG. 3.—Case 4.

All 10 patients with clinical phenomena suggesting even mild neurological complications had definitely abnormal features in their E.E.G.s, and all but two had greatly improved on subsequent examinations. The persistent E.E.G. abnormality in these two patients raised the possibility that some cerebral illness might have occurred well before the rubella.

Case 5.—A girl aged 18, who was said to be somewhat retarded but had no history of previous neurological trouble, developed a rubella rash on April 28, 1962. On May 3 she had a generalized convulsion and remained drowsy for a day. She was admitted to hospital and appeared much better the next day. Her C.S.F. contained 4 W.B.C. and 35 mg. of protein per 100 ml., and her serum electrolytes were normal. No further convulsions or disturbance of consciousness occurred while she was in hospital. The E.E.G. on the day of admission (May 3) showed a moderate but definite abnormality, with some irregular slow activity, particularly in the right temporal region. No spikes or complex wave forms were seen. In view of the peculiar appearance of the E.E.G., and of the occurrence of a seizure followed by prolonged drowsiness, further E.E.G. studies were made on May 4, 9, 16, June 13, and July 16: all showed similar features with neither amelioration nor deterioration. The patient remained well, but on account of a minimal right-sided weakness noticed on admission, and the somewhat unexplained E.E.G. findings, she was more fully investigated with air studies, but no gross cerebral lesion was detected, and psychometric testing reported an I.Q. of 111. She was discharged, but in February, 1963, was found in bed in a deep sleep, having been incontinent. No febrile illness had occurred on this occasion. An E.E.G. taken at this time showed the same type of abnormality seen in all the previous records. It was concluded that some cerebral lesion was probably present in the depth of the right hemisphere, the first known seizure having occurred eight days after the appearance of the rubella rash. It was difficult to determine how much of the neurological disorder could be attributed to rubella, whether rubella had precipitated the symptoms of a pre-existing cerebral lesion, or whether it was a chance occurrence.

Of the remaining 13 patients in whom E.E.G. studies were carried out at the time of the rash, with apparently

uncomplicated rubella, no obvious E.E.G. abnormality was found in nine; but some abnormality was found in four cases, without other detectable abnormal neurological signs or symptoms. Subsequent E.E.G.s showed no substantial change in these four patients. The features of the E.E.G.s, both in the acute stages and later, suggested that the E.E.G. abnormality might have been related to some pre-existing cerebral disorder.

Case 6.—A nurse aged 27, who denied having had any previous neurological illness, developed a rubella rash on May 27, 1962, and made a rapid recovery. The first E.E.G., taken on May 30, showed a definite generalized abnormality, with frequent paroxysmal changes, unaccompanied by clinically recognizable seizures (Fig. 4). This type of E.E.G. abnormality

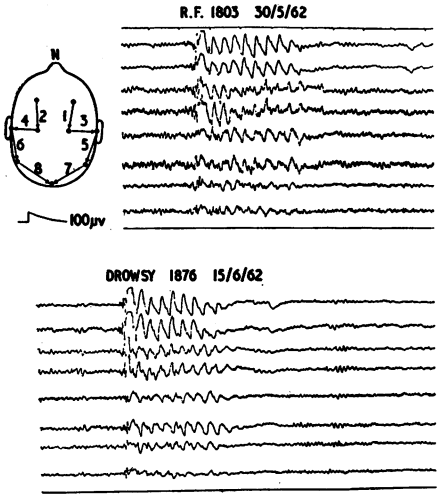

FIG. 4.—Case 6.

persisted unchanged on June 1 and 15. In view of the denial of previous neurological disorder it was decided not to pursue the matter further, and she was not informed of the possible implications of her abnormal E.E.G.

Discussion

In the rubella epidemic of 1962 two patients who had severe acute encephalitis with convulsions, coma, and gross E.E.G. abnormality made an excellent recovery (Cases 1 and 3). Another patient (Case 2), with an ascending myelitis and probably no severe encephalitis, made only a partial recovery. We can offer no satisfactory explanation for the course of the illness in these patients. It has been previously suggested that in contrast with measles the neurological complications of rubella resolve rapidly. It is possible that the cerebral lesions might differ from those of measles and be more readily reversible (Mitchell and Pampiglione, 1954), but this hypothesis is not supported by Miller *et al.* (1956).

In our patients the improvements of both clinical and E.E.G. features were at first parallel, but in general, despite an apparently complete clinical recovery, some moderate residual E.E.G. abnormality persisted in those patients who had a severe cerebral illness.

Systematic serial E.E.G. investigations were found of value in patients examined in the early phases of their rubella, whether with or without neurological complications. Particular abnormal features in the E.E.G. persisting unchanged both in the early and subsequent phases of an uncomplicated rubella suggested the presence of some pre-existing cerebral abnormality (see Cases 5 and 6). In none of the patients with either mild or severe signs of an encephalitis were there spikes or complex discharges in the E.E.G., even when seizures had occurred. On the basis of a study on a much larger series of patients with acute encephalitis by one of us (G. P.) it seems probable that the appearance in the E.E.G. of isolated spikes or complex wave-forms during an acute illness like rubella might be related to some pre-existing abnormal state of the brain. The type of the E.E.G. abnormality is of importance in the evaluation of the clinical features in the early phases of an acute illness. The lack of E.E.G. abnormalities in the majority of patients with uncomplicated rubella contrasts with what seems to happen in measles, although the age distribution of the two diseases might be an important factor. An accurate and careful timing of clinical observations and E.E.G. studies might help us to understand the complexity of the course in an apparently mild illness like rubella in patients with some pre-existing cerebral disorder (see Cases 5 and 6). Long-term clinical and E.E.G. follow-up studies in a variety of infectious diseases, well studied in the acute phases, might eventually disclose possible differences in both the transitory and the permanent neurological disabilities following specific exanthemata.

Summary

Neurological complications in rubella may be more common than is generally believed, if systematic observations are carried out throughout the course of the illness, and phenomena such as drowsiness, headache, seizures, and vomiting are considered (in addition to the more obvious signs of gross motor or mental impairment).

Systematic E.E.G. studies, in selected patients, have helped in the reassessment of the clinical evolutions of the disease, in particular instances. Seven patients with mild and three with severe forms of encephalitis during the 1962 epidemic of rubella are reported. All patients but one made a full clinical recovery, although mild E.E.G. abnormalities persisted in most of them. Uncomplicated cases of rubella did not usually show E.E.G. abnormalities (in contrast with measles), either at the time of the rash or later, in patients without pre-existing cerebral trouble.

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