LANDRY-GUILLAIN-BARRÉ SYNDROME*: CARDIOVASCULAR COMPLICATIONS

TREATMENT WITH A.C.T.H. AND CORTISONE

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The clinical manifestations of the Landry-Guillain-Barré syndrome are usually confined to the nervous system, and death, if it occurs, is in most cases due directly or indirectly to respiratory failure. Occasionally, however, the disease is complicated by circulatory collapse, which has been accepted as a complication since Osler (1892) mentioned "paralysis of the heart" as a possible mode of death. In a series of 50 fatal cases Haymaker and Kernohan (1949) found that circulatory failure was responsible for the death of three patients, and Dempsey *et al.* (1948) mention one instance in five deaths occurring in a series of 15 cases. The true incidence of circulatory failure is, however, difficult to assess because of possible confusion with the more frequent terminal event of respiratory failure (Kolle *et al.*, 1952). Usually the circulatory disturbance has been ascribed to "peripheral circulatory failure" and characterized by restlessness, sweating, cyanosis, coldness of the periphery, and marked hypotension. Less often there has been hypertension (Janet *et al.*, 1941; Haymaker and Kernohan, 1949; McDowell and Plum, 1951) and, as in acute anterior poliomyelitis (Bolt *et al.*, 1951; McDowell and Plum, 1951), this is almost certainly caused by carbon dioxide retention and hypoxia due to respiratory insufficiency, and often the fluctuations in blood pressure can be related to changes in the degree of respiratory embarrassment (McDowell and Plum, 1951).

The mechanism of the disturbance characterized by hypotensive circulatory failure is uncertain, but several factors have been suggested.

Disturbances of Cardiac Rate and Rhythm.—Sinus tachycardia of 100–120 a minute and unrelated to pyrexia is not uncommon in the Landry-Guillain-Barré syndrome (Bradford *et al.*, 1919; Radermecker, 1944); it may occur at any stage of the disease, but particularly terminally and when the neurological involvement is at its height (Susman and Maddox, 1940). A supraventricular tachycardia of 190 and auricular flutter and fibrillation have also been reported (Bradford *et al.*, 1919; Johnson, 1949; MacNeal and Bland, 1950; Wilkins, 1953). These arrhythmias have been related to respira-

tory insufficiency, involvement of the myocardium, and lesions in the autonomic nerve supply to the heart.

Involvement of the Myocardium.—In the 50 fatal cases of the Landry-Guillain-Barré syndrome described by Haymaker and Kernohan (1949), seven were found to have myocardial lesions at necropsy, but only one death appears to have been due to cardiac failure (Case 27). Although the oft-quoted case of McIntyre (1937) must be discounted because diphtheria cannot be excluded, other authors have described electrocardiographic evidence of myocarditis (Hand and Rudoy, 1948; Klein, 1954) and diffuse interstitial infiltration of the myocardium with mononuclear and polymorphonuclear cells, as well as necrosis of the muscle fibres (Péhu and Dechaume, 1927; Sabin and Aring, 1941; Klein, 1954). Similar myocardial changes are not uncommon in poliomyelitis (Teloh, 1953; and others).

Involvement of the Autonomic Nervous System.—Cardiovascular complications of the Landry-Guillain-Barré syndrome may occur in association with involvement of the brain stem (Guillain, 1936). Roseman and Aring (1941) have described pathological lesions in or near the vagal nuclei, and, although no clinico-pathological correlation has been made, several authors attribute the cardiovascular abnormalities in their patients to involvement of the vagal centre (Johnson, 1949; MacNeal and Bland, 1950; Wilkins, 1953).

Histological changes have also been reported in sympathetic ganglia and nerves (Radermecker, 1944; Haymaker and Kernohan, 1949), but no association has been noted with the clinical manifestations.

The present communication is concerned with the circulatory failure which occurred in three patients with the Landry-Guillain-Barré syndrome. One of them (Case 2) seemed to benefit greatly in respect of both the neurological disturbance and the cardiovascular complication from treatment with cortisone, and the effect of corticotrophin (A.C.T.H.) and cortisone on the disease is discussed.

Case 1

A housewife aged 63, who had suffered from chronic bronchitis for many years, was admitted to Hammersmith Hospital on February 10, 1953, and died six days later. Three weeks before admission she had nasal catarrh and a sore throat, associated later with a productive cough. She was recovering when, ten days before admission, she noticed weakness of the legs, arms, and hands. Her calves ached, she had paraesthesia in the finger-tips, and her hands were clumsy.

Examination.—She was obese and anxious. Her mental state was normal, but her intelligence was low. The cranial nerves were normal. Although all movements were possible, the limbs showed severe symmetrical weakness, more marked proximally. Respiratory movements were poor and the power of the abdominal muscles could not be evaluated accurately because of the obesity. All tendon reflexes were absent and the plantar responses flexor. Vibration and postural senses were impaired in the feet, but, so far as could be assessed, other modalities were normal. She was apyrexial but had a persistent regular tachycardia of 90 to 106. The apex beat was not defined, but the impulse suggested some left ventricular hypertrophy. The blood pressure was 170/120 mm. Hg. Scattered rales were heard over the lung fields.

Investigations.—The only abnormality in the cerebrospinal fluid was a protein content of 90 mg. per 100 ml. The blood sedimentation rate was 15 mm. in one hour (Westergren). A throat swab showed no pathogens (including *C. diphtheriae*). The urine was normal.

Progress.—Penicillin (500,000 units intramuscularly six-hourly) was given throughout. On the third day after

*Landry's paralysis and the Guillain-Barré syndrome are not distinct entities, but are manifestations of a number of clinically indistinguishable diseases. To avoid confusion in terminology, the name Landry-Guillain-Barré syndrome, as proposed by Haymaker and Kernohan (1949), should be employed until more precise knowledge regarding aetiology is available.

admission respiratory movement was limited to the upper intercostal and accessory muscles, and assistance was given with a Paul-Bragg respirator. This was used rather than a Both apparatus because the patient became distressed when lying flat, on account of her obesity and chronic bronchitis. The development of dysphagia necessitated tube feeding. Respiratory paralysis became more pronounced, and sticky sputum which she could not expectorate further impaired her breathing. Repeated aspiration of mucus from the trachea and bronchi was necessary to maintain an unobstructed airway. On her fifth day in hospital she was put in a Both respirator, but was unable to synchronize her remaining respiratory activity with the machine, and had to be returned to the Paul-Bragg apparatus and given continuous oxygen inhalation. At this time her alkali reserve was 20.5 mEq per litre.

After 17 hours of severe respiratory difficulty her condition suddenly deteriorated. She became comatose, with pin-point pupils. The pulse rate was 72 and the blood pressure 70/0 mm. Hg, although her respiratory function had not deteriorated further and her face showed a bright pink flush. As it was thought possible that she was suffering from carbon dioxide retention, the oxygen was discontinued and she slowly regained consciousness. However, the picture remained one of "peripheral circulatory failure" and the blood pressure became unrecordable. Intramuscular methedrine and an intravenous infusion of noradrenaline produced only a transient rise in blood pressure, and the patient died in deep terminal cyanosis 11 hours after the collapse.

Post-mortem Examination.—Abnormal findings were few. **Heart:** the myocardium was healthy despite severe atheroma of the coronary arteries; the right ventricle was slightly dilated, and there was hypertrophy of both ventricular walls; no histological evidence of myocarditis was found in the sections examined. **Lungs:** tracheitis, mucus in the bronchi, and oedema of the lower lobes were found. **Kidneys** showed senile arteriosclerosis. **Liver:** there was increased round-cell infiltration of the portal tracts. **Brain:** sections of the medulla and pons were normal at all levels. **Spinal cord and roots:** sections from many levels stained with haematoxylin-eosin, Weigert-Pal, and Marchi techniques, as well as frozen sections for fat, were normal. The posterior nerve root ganglia of T5 and T12 were also normal. **Autonomic system:** the thoracic chain was normal on histological examination. **Peripheral nerves:** a variety of nerves from the arms and legs showed nothing abnormal.

Comment.—There seems to be little doubt that this patient was an example of the Landry-Guillain-Barré syndrome. She presented a difficult therapeutic problem because even before respiratory paralysis developed she had hypertension and her pulmonary function was limited by obesity and chronic bronchitis. The terminal event was circulatory failure. The inability to demonstrate any pathological findings in the nervous system by the limited methods at present available is not unusual; absence of histological changes was also noted by Thorner *et al.* (1940) in more than 30% of cases of Landry's paralysis.

Case 2

A trackman on the London Underground, aged 45, was admitted to Hammersmith Hospital on February 3, 1953. One month previously he had noticed a dull pain in his lower back which radiated down the backs of his legs to the ankles. It had the characteristics of root pain, and gradually increased in severity. For three weeks he had experienced constipation and hesitancy of micturition as well as intermittent paraesthesiae in his left arm.

Examination.—He was an obese cheerful man with abnormalities confined to his legs. The quadriceps were weak on both sides, and all reflexes were absent, whereas in the arms they were brisk and equal. The plantar responses were flexor. There was indefinite hypalgesia and hypaesthesia in the right leg peripherally. The cardiovascular system was normal except for a persistent tachycardia of 90–100 and a blood pressure of 140/100.

Investigations.—The C.S.F. pressure was 200 mm. water; there was no manometric block. The C.S.F. contained 4 lymphocytes per c.mm.; protein 300 mg. per 100 ml.; the Wassermann reaction was negative; the Lange test showed no change. X-ray films of spine and chest were normal. The blood Wassermann and Kahn reactions were negative; the sedimentation rate was 12 mm. in one hour (Westergren). The urine was normal, there being no increase in coproporphyrin and no porphobilinogen or uroporphyrin. The electrocardiogram was normal.

Progress.—Within a week the leg weakness had involved all muscle groups and the arm reflexes had disappeared. His progress was now slowly downhill, and over the next month his limbs and trunk became completely paralysed and more definite sensory changes were detected peripherally in the limbs. Even when the quadriplegia was at its maximum there was no cranial-nerve involvement and respiratory function was satisfactory despite some weakness of the intercostal muscles. The diaphragm was never affected. Micturition was at times difficult, but catheterization was not required. A pyruvate metabolism test at this time was normal.

In the eighth week of his illness, when the limb and trunk paralysis was at its maximum, the patient had an attack of nocturnal breathlessness, precipitated by slipping off his pillows. Nevertheless, respiratory function was still good. The pulse rate rose to 120 and the blood pressure was 120/80. A few hours later his condition deteriorated rapidly and he went into a state of peripheral circulatory failure. Respiration was normal, but the pulse was 110 with frequent extrasystoles. The blood pressure was unrecordable and the peripheral pulses could not be felt. He was mentally confused and very restless, was slightly cyanosed, and his skin was cold and clammy. Up to the time of this sudden collapse renal function had been normal. An E.C.G. showed a nodal tachycardia of 100–110, elevation of the ST segments in Leads V₄₋₆, and tall gothic T waves in Leads II and III and V₄₋₇ changes consistent with hyperkalaemia (Fig. 1).

He seemed to be dying. In order to determine whether the circulatory state was due to a low cardiac output or to a reduction in peripheral resistance, a catheter was passed into the right atrium, oxygen consumption was measured with a spirometer, and a needle was inserted into the brachial artery. Oxygen consumption was 400 ml. a minute, in keeping with his restlessness. The arterial blood contained 15.6 volumes of oxygen per 100 ml. (78% saturated) and the mixed venous blood contained 6 volumes (30% saturated). The cardiac output was 4.2 litres a minute (a low figure in relation to his metabolic needs). The pressure in the right atrium was raised above normal (+8 mm. Hg) and the pressure in the brachial artery was 90/80 mm. Hg. The peripheral resistance was 1,620 dynes sec. cm.⁻⁵, which is not strikingly lower than normal, and there was no evidence of a significant loss of peripheral vascular tone. Analysis of a venous blood sample at this time showed a raised potassium concentration of 6.8 mEq per litre, a reduced sodium of 125 mEq per litre, chloride normal at 98 mEq per litre, CO₂-combining power 20 mEq per litre, and glucose 145 mg. per 100 ml.

The patient was digitalized with 1 mg. of digoxin intravenously, followed by 0.5 mg. six-hourly by mouth, and was also given 75 mg. of cortisone six-hourly by mouth. Within seven hours there was a striking improvement in his condition. He was warmer, rational, and less cyanosed, with complete absence of his earlier restlessness. The pulse rate had fallen to 100 and the blood pressure had risen to

FIG. 1.—Case 2. E.C.G.; Lead V₄ during the circulatory failure.

120/60. During the next day the jugular venous pressure returned to normal. The pulse rate persisted at 110 and the blood pressure rose to 130/85. The E.C.G. (Fig. 2) showed changes due to digitalis, but the T waves were now normal. The serum potassium was 4.7 and the sodium 131 mEq per litre.

Four days after this acute episode improvement in muscle power was noted for the first time. One month later he could sit up unaided, and after two months he could walk with support. The weakness disappeared in the reverse order of its appearance. He was discharged six months after the onset of his illness; sensation was normal, but there was still slight bilateral weakness of foot dorsiflexion, and all the tendon reflexes were absent. One year later he had no complaints, his cardiovascular and nervous systems were normal, and he had returned to work.

FIG. 2.—Case 2. Lead V_4 after recovery.

Comment.—This case is an example of the slowly progressive type of the Landry-Guillain-Barré syndrome. The muscle weakness was not maximal until the eighth week of the illness, and it was at this time that the acute circulatory failure occurred.

Case 3

A company executive aged 30 was admitted to the National Hospital, Queen Square, on April 8, 1954. Ten days before, in Khartoum, he had developed back pain, headache, and neck stiffness. There had been no preceding illness. Weakness of the limbs developed rapidly and it became necessary to aid respiration.

Examination.—He was slightly cyanosed and sweating. There was severe weakness of limb and trunk muscles, only slight diaphragmatic movements being present. All tendon reflexes were absent and peripheral sensory changes were found. The cardiovascular system was normal; blood pressure was 150/90 and pulse rate 60 to 80.

Investigations.—The only abnormality in the C.S.F. was a protein content of 350 mg. per 100 ml. The blood serum electrolytes and alkali reserve were normal. The E.C.G. was normal.

Progress.—The patient was treated in a Siebe-Gorman respirator, but he improved steadily and within a few days could be weaned from the apparatus. Two months after admission his respiratory function had improved (vital capacity 1 litre) and the power of his limbs was increased. However, without any apparent neurological, cardiovascular, or respiratory change, he had periods of altered personality. During one of these, on June 29, he became confused and irrational, the heart sounds were faint, and a pericardial friction rub was heard. His blood pressure was normal, but the pulse rate had risen to 120–140. The E.C.G. showed flattening of the T waves in all leads but no displacement of the ST segments. There was increased weakness of the limb and intercostal muscles. The vital capacity fell to 400 ml. and he was placed in the respirator again. Five hours later he began to show signs of circulatory failure; his blood pressure was 85/60 and the pulse thready. Serum electrolytes and urinary output were normal both before and during this episode.

He was given 300 mg. of cortisone by mouth during the next 24 hours and thereafter 50 mg. daily. An intravenous infusion of plasma containing 80 mg. of noradrenaline per 500 ml. was begun, and the rate was adjusted to maintain a blood pressure of 120/80. After 13 hours the infusion was discontinued, following which there was a transient fall in blood pressure with tachycardia lasting about two hours.

Recovery now began to take place, and it was soon possible to remove him from the respirator for increasing periods. Four months later he was improving slowly, but some limb weakness persisted and his vital capacity was still low (1,200 ml.).

Comment.—In this case the illness in its early phase was typical of the Landry-Guillain-Barré syndrome. It was, however, complicated by a recrudescence of respiratory paralysis associated with pericarditis and circulatory collapse.

Discussion

In all three of these patients the Landry-Guillain-Barré syndrome was complicated by circulatory collapse, the predominant feature of which was hypotension. The precise mechanisms for this disturbance remain uncertain, nor is it clear that the same factors were responsible in each case.

In Case 3 the circulatory failure was associated with a recrudescence of muscular weakness and the development of a pericardial friction rub. This suggests that the relapse was due to a reactivation of the disease process which involved the pericardium and also the myocardium, since the circulatory failure and hypotension are not usual features of acute pericarditis. Although respiratory failure also occurred at this time, there was no biochemical evidence of carbon-dioxide retention or depletion, and no circulatory disturbance had occurred when the respiratory insufficiency was equally severe in the earlier phases of the illness.

In Case 2 there was evidence of disturbed myocardial function, which occurred at the time of maximum neurological involvement and which was unassociated with any respiratory muscle failure. The onset of the circulatory disturbance was heralded by an attack of nocturnal dyspnoea, presumably due to left ventricular failure, and followed by severe hypotension and impalpable peripheral pulses. The cardiac output of 4.2 litres a minute was low when considered in relation to the patient's size, the extreme degree of restlessness, and the marked unsaturation of mixed venous blood indicating that the tissues were extracting an unusually large amount of oxygen from the circulating blood. Although there was a nodal tachycardia of 110 this was neither sufficiently rapid nor sufficiently prolonged to be the cause of the heart failure, and, when the circulatory collapse had improved, the heart rate remained rapid for several days without evidence of cardiac failure.

An important finding was the hyperkalaemia and the hyponatraemia. Potassium intoxication can cause a circulatory state indistinguishable from that presented by the patient, but he was not receiving more than the normal dietary intake of potassium, and his renal function and urine output were normal until the time of the acute episode. The electrolyte disturbances could have been a primary event in the circulatory disturbance if the patient was suffering from acute adrenal insufficiency, or if large amounts of potassium were being liberated from the paralysed muscles into the extracellular phase. We have no data to confirm or exclude these possibilities. Sabin and Aring (1941) have described histological changes in the suprarenal glands of patients dying with the Landry-Guillain-Barré syndrome, but in their 50 fatal cases Haymaker and Kernohan (1949) did not find significant adrenal abnormalities.

Hyponatraemia occurs not uncommonly in heart failure following treatment with mercurial diuretics (Stock *et al.*, 1951; Welt, 1952) and in myocardial infarction even before treatment of any sort has been given. In these cases the serum potassium concentration is usually low, but Bellet (1952) has encountered hyperkalaemia in patients with myocardial infarction, and attributes this to breakdown of the necrotic lesion in the heart, dehydration, and the shock-like state with coexistent oliguria. Thus it is difficult to decide whether the hyperkalaemia in this patient was a primary event and responsible for the circulatory collapse or secondary to involvement of the myocardium by the disease process. The response to digoxin and cortisone was dramatic. The former would be expected to improve the

myocardial function and the latter to correct the electrolyte disturbances and perhaps influence the disease process in the heart muscle. Within seven hours the patient's moribund condition had improved greatly, and it is reasonable to believe that a large part of this response was attributable to the effect of cortisone.

The first patient was older than the others, and handicapped by obesity, chronic bronchitis, and hypertension. It is possible that coexistent heart disease may explain the higher mortality in older patients who develop the Landry-Guillain-Barré syndrome—for example, Case 7 of Lassen and Fog (1943). The onset of circulatory failure coincided with maximum involvement of the nervous system and occurred after 17 hours of respiratory difficulty. The post-mortem findings were not helpful in elucidating the mechanisms involved, and in the absence of apparent myocardial involvement it remains uncertain whether carbon dioxide retention or further extension of the disease process in the brain stem (as suggested by the pin-point pupils and comatose state) was of importance.

The improvement in the cardiovascular state of Case 2 may in part have been due to treatment with cortisone, and recovery of muscular power also began to occur following cortisone in Cases 2 and 3. If, as has been suggested (Bannwarth, 1943), the Landry-Guillain-Barré syndrome is due to a hypersensitivity reaction of the nervous system rather than to a virus infection, the use of A.C.T.H. or cortisone seems reasonable on the analogy with rheumatic fever. Evaluation of the response is difficult because the course of the disease is variable and spontaneous remissions and relapses are common.

Since 1952 the results of treatment with A.C.T.H. or cortisone have been reported in 46 cases of the syndrome. In 10 cases in which the drug was ineffective details are not available (Merritt, 1952; Eaton, 1953; Plum, 1953). A further eight cases were associated with specific diseases such as infectious mononucleosis or polyarteritis nodosa (Wilkins, 1953; Fiese *et al.*, 1953; Plum, 1953; Plough and Ayerle, 1953; Stýblová and Dejmál, 1953; Liversedge and Leather, 1953). The remaining 28 cases had the usual clinical picture (Seltzer *et al.*, 1952; Stillman and Ganong, 1952; Tolentino, 1952; Newey and Lubin, 1953; Blood *et al.*, 1953; de Assis and Netto, 1953; de Assis, 1953; Senseman and Greenstein, 1953; Vernon, 1954; Lúzes, 1954; Gilsanz *et al.*, 1954; Tupper and Foster, 1954; Essellier and Kopp, 1954; Foster and Pokorny, 1954; Guiang and Leones-Guiang, 1954; Bolt *et al.*, 1954). Nine, of whom five had bulbar involvement, showed dramatic improvement; in 12 the progression of the disease was halted and improvement took place; and in the remainder no change occurred. None appear to have been made worse. One patient relapsed while receiving A.C.T.H., but improvement occurred again when cortisone was given (Stillman and Ganong, 1952), and in two patients Plum (1953) was able to demonstrate the beneficial effects of cortisone as compared with a placebo.

Thus it seems that treatment with corticosteroids deserves further consideration, despite the objections of Guillain (1953) and in spite of the fact that Grant and Leopold (1954) have described a patient who, while receiving an adequate dose of cortisone for rheumatoid arthritis, developed the Landry-Guillain-Barré syndrome. At present perhaps such treatment is indicated only in patients showing relentless deterioration, having relapses, or in those with hypotensive cardiovascular collapse; spontaneous recovery from the latter, however, has been observed (Smith *et al.*, 1954). Its use should also be considered in patients with bulbar involvement and respiratory failure, although recovery without treatment in even these cases is frequent. There is not enough evidence to indicate whether cortisone influences the outcome of the straightforward case, but it is possible that recovery may be accelerated and pain relieved (Stillman and Ganong, 1952; Lúzes, 1954; Foster and Pokorny, 1954). The steroid should be given in divided oral doses of 300 mg. during the first day, 200 mg. during the second, and 100 mg. daily thereafter. Since those patients who have responded

dramatically have all been given the hormone early in the course of their disease, the institution of treatment should not be delayed.

When the clinical picture is complicated by circulatory collapse it is suggested that involvement of the myocardium rather than loss of peripheral vascular tone may be the cause. For this reason an infusion of noradrenaline should be given to combat the hypotension, together with digoxin and cortisone in the belief that these may improve the myocardial function and perhaps favourably influence the pathological process.

Summary

Three cases of the Landry-Guillain-Barré syndrome complicated by acute circulatory failure, which was fatal in one patient, are reported.

Evidence is presented to suggest that in some cases myocardial dysfunction is responsible for the circulatory complications.

The value of adrenocortical steroids in the uncomplicated disease is reviewed, and suggestions are offered for the treatment of the circulatory collapse.

There is some indication that cortisone may influence the course of the disease favourably, and further experience is justified.

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