

LANDRY-GUILLAIN-BARRÉ SYNDROME

Treatment with ACTH and Cortisone

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Landry paralysis and the Guillain-Barre syndrome are not distinct entities and the differentiation, between these two diseases, is artificial (Lewy, 1945). Haymaker and Kernohan (1949) in their review on these diseases, supporting Lewy's view, proposed a new terminology of Landry-Guillain-Barre syndrome. Landry in 1859 made the earliest description of the Guillain-Barre syndrome. Osler in 1892 described a febrile illness followed by paralysis and attempted to differentiate it from Landry's paralysis. Kennedy, following his World War I observations, pointed to proximal weakness and distal sensory loss. Guillain, 1936, reviewed his observations and emphasized its favourable prognosis. The outcome of the disease is not always favourable. The common cause of death is respiratory failure, but occasionally cardio-vascular complications do occur, resulting in acute circulatory collapse with hypotension. Haymaker and Kernohan (1949) found circulatory failure responsible for the death of three patients in 50 fatal cases. Sometimes spontaneous recovery can occur without fatality.

In the present clinical material three cases have been described which differ from classical description in selective muscular weakness and sensory distribution. These have been treated with ACTH and Cortisone.

CASE REPORTS

Case 1

History. Housewife, aged 28, was admitted on November 26, 1954, and died on December 18, 1954. The history revealed that she was well six days previously when, after a mild attack of respiratory infection, sore throat and malaise; she developed headache and also pain down the back of the legs to the ankles, with the characteristics of root pain. Her calves ached, and she felt numbness in the hands and feet. These symptoms were followed by gradual weakness of the legs and arms.

Examination. C.N.S.: her speech was slurred.

(a) **Cranial nerves:** within normal limits. There was nuchal spasm on flexion of the neck. **Motor:**

all muscles of the upper and lower limbs were weaker in the proximal segments of the upper limbs. distal segments were involved more in the legs. The weakness was symmetrical in the upper limbs and asymmetrical in the lower limbs. Trunk muscles were also involved, sparing the bulbar and peripheral respiratory muscles. **Sensory:** all sensory modalities were lost with definite sensory level up to C5 and D10. **Reflexes:** all the deep jerks were absent in the legs, just present in the upper limbs. The abdominal reflexes were absent and plantar reflexes were not elicitable. **Co-ordination:** marked ataxia on finger-nose test this was not demonstrable in the legs due to marked weakness in the legs. **Bladder:** hesitancy of micturition was complained. **Bowels:** constipated. Peripheral arteries were perceptible.

(b) **General.** Pulse 80 p.m. regular in rhythm, fair volume and amplitude. Blood pressure 105/60. No significant abnormality was detected on systemic examination. She was running intermittent pyrexia (98 to 100°F.) during hospitalization, which settled down in three days.

Investigations. Haemoglobin: 66 per cent. R.B.C.s: 3,580,000 per c.mm. W.B.C.s: 7,450 per c.mm., (polymorphs: 79 per cent.; lymphs: 16 per cent.; monocytes: 5 per cent). E.S.R. 135 mm. per hour. Blood urea: 15 mg. per 100 ml. Serum Protein: 4.9 g. per cent. (albumin 3.4 g. per cent; globulin: 1.5 g. per cent). Urine analysis: nothing abnormal was noted and uroporphyrins were not detected. Urinary ketosteroids: 11.4 mg. per day before ACTH. C.S.F.: Clear fluid, normal dynamic, cells 80 per c.mm., protein 90 mg. per 100 ml., globulin was present. Culture negative and W.R. was also negative. Lange: 000000000. **X-ray** of chest showed enlarged heart in transverse diameter, and lungs clear. **X-ray** of dorsal and lumbar spine, was normal. **Biopsy** of muscle was normal. No evidence of polyarteritis or other abnormality was noted.

Diagnosis. In view of the history and findings diagnosis of Landry-Guillain-Barré syndrome was made.

Progress. The patient was given a course of Aureomycin (500 mg. to start with, then 250 mg. six-hourly). On November 30, 1954, she developed bilateral ptosis, blurred vision, defective hearing, tinnitus, hesitancy in micturition and constipation. Now flaccid paralysis was marked in the legs; still there was some movement in the peripheral segments of the upper limbs. Sensory loss remained at the same level. On December 3, 1954, she developed L.7 n. palsy (lower motor neurone). Sensory level progressed up to D2 in segmental type. Reflexes in the upper limbs were absent. She developed urinary retention, requiring catheterization. On the same day she was put on ACTH Gel. 20 units b.d. Three days later (December 6, 1954), she developed frank haematuria with back ache. A diagnosis of polyarteritis or acute nephritis in association with Landry-Guillain-Barré syndrome was considered and she was put on acute-nephritic diet regime with combination of ACTH Gel. 20 units b.d. and a course of streptomycin g. $\frac{1}{2}$ b.d. for urinary tract infection. The catheter specimen of urine showed alkaline reaction, albuminuria ++, R.B.C.s +++, polymorphs ++, granular casts +. Culture: B. Proteus, sensitive to chloromycetin, not sensitive to streptomycin, penicillin, and weakly sensitive to aureomycin. She was put on a course of chloromycetin and streptomycin was discontinued. Now blood urea was 48 mg. per cent. Haematuria continued and the blood urea was gradually raised up to 87 mg. per cent., and there was no improvement in the clinical condition. On December 12, 1954, ACTH was reduced to 20 units daily. The only improvement was the complete recovery of the 7th n. palsy, ptosis, and some power was noted in the proximal group of muscles of the upper limbs. There was no improvement in sensory loss, blurring of vision, tinnitus, legs and trunk muscles paralysis. Her blood pressure was 140/90. There was no evidence of cardiovascular or respiratory insufficiency. On December 13, 1954, blood urea was 144 mg. per cent; haemoglobin: 90 per cent.; E.S.R.: 70 mm. per hour. W.B.C.s: 13,150 per c.mm. Haematuria was still present. ACTH was discontinued on December 15, 1954. Twelve hours later she developed sudden circulatory collapse with sweating and restlessness. Pulse was 140 p.m., weak and thready. Blood pressure was 90/60. She was treated by intra-venous Glucose/Saline and Oral Cortisone, 25 mg, six-hourly. She died suddenly in acute pulmonary oedema after some temporary recovery.

Necropsy: bilateral extensive supra-renal cortical haemorrhages with necrosis (vacuolation), cystitis and pyelonephritis. No abnormality was noted in other systems, or in C.N.S.

Comment. This patient appeared to have had severe Landry-Guillain-Barré syndrome associated with fatal adrenal failure due to massive bilateral suprarenal haemorrhage.

Case 2

History. Male, aged 57, was admitted to North Lonsdale Hospital on May 2, 1955. History revealed that two weeks previously he had had a sore throat which was followed by pain in the back radiating down into the legs, associated with numbness in the hands, and pins and needles in the legs.

Examination: He was a well nourished man with clear mentality. Cranial nerves were normal. He had extensive flaccid quadriplegia with involvement of the neck and trunk muscles as well. Paralysis was marked in the proximal segments of the upper limbs, but in the legs the distal segments were involved more than the proximal. There was an asymmetry in paralysis on the two sides. He was unable to sit up without support and expectorate properly. All deep reflexes were absent; abdominal and plantars were not elicitable. Sensory loss to pin-prick, touch, vibration and joint sense was present in the periphery of the limbs with gloves and sock distribution. He could appreciate temperature. There was marked ataxia on finger-nose test. Sphincters were normal.

General examination: pulse 120° per minute. Later on tachycardia of 100 to 90 was persistent for four weeks. Blood pressure was 130/60. Cardiovascular and respiratory systems were normal.

Investigations. C.S.F. was clear, its dynamic was normal and it contained 2 cells per c.mm., protein 200 mg. per 100 ml., globulin was present, Lange normal, W.R. and culture were negative. Serum electrolytes were normal. X-ray of chest and spine revealed no abnormality. Urinary 17 ketosteroids were 9 mg. per day. E.C.G. showed prominent 'T' waves (7.5 mm. in height).

Progress and Treatment. In view of the flaccid quadriplegia with polyneuritis and albumino cytologique dissociation in the C.S.F., a diagnosis of Landry-Guillain-Barre syndrome was made. He was given cortisone, 300 mg. on the first day, 200 mg. on the second day, and thereafter 100 mg. daily. No appreciable change was noted. He was given estopen/penicillin 500,000 units b.d. to avoid chest infection. Two weeks later cortisone was changed to ACTH (Armour) Gel. 60 units b.d. as there was no improvement while on cortisone. After 48 hours on ACTH injections, his urinary 17 ketosteroids were increased to 16 mg. per day (previously being 9 mg. per day). Within three days of ACTH treatment he showed remarkable

improvement in his power. His grip was better and he started moving the upper limbs and legs. He was able to sit up and in a few days was able to feed himself. His power of expectoration was satisfactory. A week later ACTH Gel. was reduced to 40 units b.d. which was continued for four weeks and then was further reduced to 20 units b.d. for another two weeks. He maintained the recovery with gradual improvement, which was hastened by physiotherapy. ACTH was discontinued after six weeks. He made a remarkable recovery in his motor power and sensory loss and now is able to walk with aid but has some foot drops, more on the left. Muscles wasting was noted in both limbs. Six weeks later, he went home walking as a normal person, without aid, with complete recovery.

Comment. This case presents features of Landry-Guillain-Barré syndrome with unusual asymmetrical paralysis and involvement of the distal parts of the legs more than proximal, tachycardia and normal adrenal functions, proved by ACTH test.

Remarkable recovery was noted after treatment with ACTH in motor paralysis and sensory loss, except vibration sense.

Case 3

History. A man aged 59, was admitted to the North Lonsdale Hospital for flaccid paraplegia and weakness of the upper limbs, on August 11, 1955. He was well until two weeks previously when he had an attack of 'flu,' and a week later he developed sudden loss of power in the legs, weakness in the arms, associated with pins and needles in the limbs, preceded by pain in the back of radicular type.

Examination. His general condition was fair. Pulse 100 p.m. regular, volume fair. Blood pressure 135/80. Temperature 100°F. C.N.S.: mental state was fair, cranial nerves were normal. *Motor:* some weakness in the upper limbs with marked flaccid paraplegia and involvement of the trunk muscles (patient was unable to sit up with support). Flaccid paralysis was asymmetrical. Peripheral segments were involved more than proximal and left leg and foot were more weaker than right. *Sensory:* there was sensory loss of gloves and socks type in the limbs for pin prick, touch, temperature and vibration. *Reflexes:* all reflexes were absent. Plantars were flexor. Sphincters were normal. *Systemic general examination:* revealed no relevant facts.

Investigations. F.B.C., E.S.R., blood urea, and serum electrolytes were all within normal limits. Urine examination revealed no abnormality. C.S.F.: dynamic normal; cells: 2 lymphs. per c.mm.; protein: 1,000 mg. per 100 ml.; globulin

+; lang: 1112344320; W.R.: negative. Urinary 17 ketosteroids were 11.2 mg. per day. Blood eosinophils 194 per c.mm., before ACTH. Seventy-two hours after ACTH (60 units. Gel. b.d.) 17 ketosteroids were 34 mg. per day and eosinophils: 37 per c.mm. E.C.G. revealed no abnormality. In view of the extensive paralysis, sensory changes and definite albumino-cytologique dissociation Landry-Guillain-Barre syndrome was diagnosed. He had persistent tachycardia of 90 to 100 which lasted for four weeks. His adreno-cortical function was normal.

He showed no signs of improvement during the first week of hospitalization so ACTH course was started on August 19, 1955. ACTH Gel. 60 units b.d. was given for one week, 40 units Gel. b.d. for the next week and 20 units b.d. for one week, and 10 units b.d. for the fourth week, then was discontinued.

Progress. After three days of ACTH injections a remarkable improvement was observed in his motor power. On August 23, 1955, there was 50 per cent. improvement in the power of the legs with free movement, and on August 25, 1955, he was able to sit up in bed without support—there was regression of sensory changes in the limbs. A week later he was able to walk with aid, with some residual weakness in peripheral groups of muscles, more on the left. At the end of the four-week course he was walking freely with aid with some foot drops, more on the left. There was no improvement in vibration sensory loss. Muscle wasting was observed in both limbs.

Comment. This Landry-Guillain-Barre syndrome patient, with normal adrenal function as proved by ACTH test and persistent tachycardia, made remarkable recovery with ACTH more rapidly than the previous patient.

Discussion

Case No. 1 presents the features of Landry-Guillain-Barre syndrome with notable absence of albumino-cytologique dissociation in the C.S.F. It is now regarded that hyperalbuminosis depends on local vasodilation, increased permeability of the dilated radicular and spinal meningeal vessels, swelling of the spinal nerves and partial block of spinal fluid by oedema of the spinal cord (Haymaker and Kernohan, 1949). In the early stage, hyperalbuminosis is absent and sometimes C.S.F. is normal (Brain, 1951).

Another unusual feature in this case was segmental type of sensory loss, which may be due to oedema of the spinal cord. Haymaker and Kernohan (1949) have described such cases in their paper. It is difficult to say whether this type of

sensory loss is due to oedema of spinal cord, radicular involvement, or extension of morbid process in spinal cord, and it is hard to conceive of such widespread and uniform loss of sensibility without implication of the spinal cord.

Pleocytosis in this case was unusual. Guillain in 1936 refused to accept hyperlymphocytosis belonging to this syndrome. Haymaker and Kernohan (1949) felt that paucity of cells is over stressed and they described cells up to 200 to 514 P.C. mm. with fluctuation during the illness. They ascribed pleocytosis to meningo-radiculo-neuritis.

It has been noted that paralysis is symmetrical. Proximal limb muscles are involved more severely than distal, a point of distinction from other forms of poly-neuritis, but this relative incidence of weakness is variable and has probably been over-stressed. In the presented cases maximal paralysis was observed in the distal muscles of legs with asymmetrical involvement, suggestive of asymmetrical mono-neuronitis multiplex.

Bilateral ptosis, bowel and bladder dysfunction could be explained by autonomic dysfunction.

The mechanism of acute circulatory collapse with hypotension is not yet settled. The suggested causes by various authorities are: cardiac arrhythmias (Johnson, 1949; McNeal and Bland, 1950); myocarditis (Haymaker and Kernohan, 1949); lesions of brain stem (Guillain, 1936), and Vagal nuclei involvement (Johnson, 1949; McNeal and Bland, 1950; Roseman and Aring, 1941). Sabin and Aring (1941) described suprarenal necrosis in three cases that died with Guillain-Barré syndrome, focal necrosis, vacuolization, focal cellular infiltration and focal phlebitis was noted by them as seen in heart and lungs. Roseman and Aring (1941) noted significant abnormality in suprarenals of three cases of Guillain-Barre syndrome. Clarke *et al.*, (195) described three cases with acute circulatory hypotensive failure. Their second case showed electrolyte disturbance, but they were unable to confirm or exclude suprarenal insufficiency and stressed on myocardial dysfunction causing peripheral circulatory failure. Haymaker and Kernohan (1949) described histological changes in sympathetic ganglion and nerves. Recent pathological and experimental observations have suggested that the isolated Fiedler myocarditis and interstitial myocarditis with cellular infiltration, as described in cases of infective polyneuritis, can occur as a result of allergic reaction and hypersensitivity to sulphadiazine, serum and arsphenamines (Friedberg, 1951). In Case No. 1 the mechanism of collapse was acute adrenal insufficiency due to massive haemorrhage.

Aetiology

Many theories have been forwarded to explain

the aetiology of Landry-Guillain-Barré syndrome. The recent view is that it is an allergic reaction and manifestations of the hypersensitivity of the nervous system as a response to various noxious agents such as upper respiratory infection, 'flu' (Furtado, 1950) faucial and cutaneous diphtheria (Delp *et al.*, 1946 and Smith, 1951) and as a toxic reaction during sulphadiazine therapy (Smith, 1951). It is also associated with infectious mononucleosis (Smith *et al.*, 1954; Raftery *et al.*, 1954; Garvin, 1953; Lawrence, 1951); brucellosis (Roger *et al.*, 1949); infective hepatitis (Zimmerman and Lowry, 1947); anti-rabies inoculation (McIntyre, 1949 and Krouse); other types of infectious diseases, and with polyarteritis nodosa (Liversedge and Leather, 1953). These conditions were associated with cyto-albuminic dissociation and various types of paralysis. Recently, post-exanthematous encephalomyelitis and various other neurological complications such as polyneuritis, Landry paralysis, neuromyelitis optica like lesions are regarded as hyperergic reaction to the original virus infection (Brain, 1951). Von Bogaert (1932-1933) regards these reactions of hypersensitivity, due to inherited deficiency in the capacity for developing immunity and lack of normal defensive reaction. Miller *et al.*, (1949) described changes in vasa nervorum of nerves as primary lesion in infective polyneuritis.

Treatment

Recently polyarteritis nodosa and other hypersensitivity states have been successfully treated by ACTH and Cortisone with improvement in polyneuritis, hence various workers have treated Landry-Guillain-Barre syndrome with ACTH and Cortisone. Blood *et al.*, (1953) reported improvement in severe symptoms within four days of beginning of treatment, in their cases. Newey and Lubin (1953) reported demonstrable improvement within 30 minutes of the conclusion of 8-hourly i.v. infusion of Corticotrophin, 25 mg. Liversedge and Leather (1953) described improvement in a case of polyarteritis nodosa with Guillain-Barré syndrome in 48 hours of commencing ACTH Gel. 25 mg. b.d. Stillman and Ganong (1952) described relapse in ACTH receiving case who responded to Cortisone. Plum (1953) treated three cases with Cortisone—two responded well and one failed to improve. Clarke *et al.*, (1954) recently reported two cases, with acute hypotensive collapse, successfully treated by Cortisone—300 mg. during the first day; 200 mg. during the second day; 100 mg. daily; and Digoxin, 1 mg. i.v. followed by 0.5 mg. 6-hourly by mouth. Smith *et al.*, (1954) described one case of Guillain-Barre syndrome who developed acute respiratory insufficiency and hypotensive circulatory collapse

which recovered without hormone therapy. Grant and Leopold (1954) described a case of rheumatoid arthritis who developed Landry-Guillain-Barré syndrome after adequate Cortisone. Eaton treated four cases of Guillain-Barre syndrome at Mayo Clinic with ACTH and one with Cortisone. None showed significant response. Meritt has treated four cases and no effect of hormone was noted. Patients who failed to respond to Cortisone or ACTH may have suffered severe direct neuronal damage either at root or at peripheral level. If nerve axons were not damaged but compressed by oedema, amelioration of root oedema by Cortisone or ACTH might explain rapid improvement, hence ACTH or Cortisone should be used as early as possible before the neuronal damage; once this has been set, ACTH or Cortisone will not improve the disease. Early use of ACTH also may relieve ischaemia by recanalizing the occluded vasa nervorum, resulted by hypersensitivity.

Summary

1. Three cases of Landry-Guillain-Barré syndrome have been described. The aetiology and pathological physiology is discussed.

2. It seems that ACTH and Cortisone can influence the course of the disease. The dose must be chosen individually for each patient according to the severity of the disease and adrenocortical function; the latter can influence the prognosis of the case.

3. Further experiences are needed to appraise the value of these hormones.

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