GUILLAIN-BARRÉ SYNDROME*

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Since publication of the paper by Guillain, Barré, and Strohl[1] in 1916 describing 2 cases of polyneuritis with albuminocytologic dissociation with a favorable result, many investigators have presented their opinions in an attempt to clarify the status of this syndrome. Unfortunately, almost every author gave his particular modification of the Guillain-Barré syndrome a new name, and as many as thirty appellations have been found in the literature. The following are examples: radiculoneuritis with acellular hyperalbuminosis of cerebrospinal fluid,[2] acute infectious polyneuritis,[3] polyradiculoneuritis with albuminocytologic dissociation,[4] acute ascending paralysis,[5] infectious polyneuritis,[6] acute encephalo-myelo-radiculoneuritis,[7] polyneuritis of unknown etiology,[8] acute polyradiculoneuritis,[9] encephalo-myelo-radiculitis,[10] infectious neuronitis,[11] polyradiculoneuritis,[12] neuronitis,[13] albuminocytologic dissociation in cerebrospinal fluid with xanthochromia,[14] polyradiculoneuritis with albumino-cytologic dissociation of cerebrospinal fluid,[15] myeloradiculoneuritis with cell protein dissociation,[16] myeloradiculitis,[17] acute polyneuritis,[18] acute infectious meningomyelo-radiculitis,[19] meningomyelo-encephalitis and meningo-radiculomyelitis,[20] polyneuritis with facial diplegia,[21] curable polyradiculoneuritis,[22] infective neuronitis,[23] peripheral neuritis,[24] chronic progressive polyneuritis,[25] polyneuritis,[26] acute diffuse polyradiculoneuritis,[27] acute polyneuritis with facial diplegia,[28] acute benign infectious myelitis,[29] acute infective polyneuritis,[30] acute febrile polyneuritis,[31] multiple neuritis,[32] toxic neuronitis of pregnancy,[33] acute polyradiculoneuronitis,[34] meningo-encephalo-myelo-neuritis.[35] In spite of the multiplicity of titles, the whole subject "is still in the formative stage and up to this time has hardly advanced beyond the detailed clinical description and possible relationships", to quote the excellent work of Taylor and McDonald[21] published in 1932.

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Although it is generally a good practice to avoid a proper name and to use an anatomic term, in this particular syndrome it would be well to abandon the multiple anatomic terms and merely to designate the composite group as the Guillain-Barré syndrome, as proposed by Lewey,[36] who said, "It is suggested that we retain the designation Guillain-Barré syndrome which has become popular as a general heading for the various forms of polyneuropathy and radiculoneuropathy of unknown etiology." Dr. LaSalle Archambault expressed this opinion well in a discussion of the paper of Strauss and Rabiner[17] when he said, "To my mind it is rather unfortunate that a new name should be coined every time a fresh group of cases arises, merely on the basis of some minor and frequently inconstant differential feature."

In 1916 Guillain, Barré, and Strohl[1] published their original paper emphasizing the albumino-cytologic dissociation with a favorable prognosis in 2 cases. They described the condition as a "syndrome characterized by motor disturbances, abolition of tendon reflexes with preservation of cutaneous reflexes, of paresthesias with minor disturbances of objective sensibility, of pain on pressure of muscles, of slight modification of electrical reactions of nerves and muscles and of albumino-cytological dissociation of cerebrospinal fluid." Their report of the dissociation was a definite milestone, but this same discordance between protein and cell count led Guillain into an error in prognosis which was not rectified in his own mind until 1937.

In 1936 Guillain[2] defended his original position and insisted on albumino-cytologic dissociation ("cases with .3—.4 Gm. [300-400 mg. per cent] do not belong to this syndrome") and a favorable prognosis. He also acknowledged the presence of facial palsy in some cases.

Finally in 1937 Guillain,[37] in a discussion of a paper by Barré, retracted his firm stand that the total protein had to be 1 to 2 Gm. (1000-2000 mg. per cent) for a diagnosis of his syndrome. He also admitted that fatal cases did occur.

Etiology

The etiology of this syndrome is just as vague and as poorly crystallized as are its manifold symptoms. In 1919 Wilson[30] believed that he had isolated and cultivated the virus and postulated that the disease could be transmitted from man to monkey and from monkey to monkey. However, this claim was soon retracted, particularly as to isolation of virus, and Collier[24] observed that the causal relation of virus infection to polyneuritis remains unproved. Guillain and Barré,[38] themselves, believed that the disease was congestive and not inflammatory. This fact explains the good prognosis they usually found in the syndrome

and the relative rapid return to the normal state. This, of course, does not exclude the possibility of a virus being a causative factor, with a predominant action of vasodilatation that is also reversible. Several authors[39] have advanced the hypothesis that a number of cases of the Guillain-Barré syndrome may actually be manifestations of anterior poliomyelitis with favorable outcome.

The fact that diseases such as diphtheria, syphilis, diabetes, toxemia of pregnancy, serum sickness, and reaction to mustard gas in isolated instances may present a clinical syndrome identical with that of the Guillain-Barré syndrome (even to the cerebrospinal fluid albumino-cytologic dissociation) would seem to point toward a toxic agent as the etiologic factor.[40]

Pathology

As to the pathology of the syndrome, analysis of numerous investigations reveals no common denominator. The most common process is a degeneration and demyelinization of the central nervous system without signs of inflammation. Small round cell infiltration which could be interpreted as a positive inflammatory phenomenon was frequently encountered. The diversity of the pathologic findings further attest the sound wisdom of regarding this condition as a syndrome rather than as an entity.

The studies of the cerebrospinal fluid furnish by far the most characteristic and constant changes, and it is probably on these that the entire complex hangs together as an entity.

Guillain *et al.*[1] originally pointed out the albumino-cytologic dissociation in 1916. That this was not necessarily constant was evident from the work of Bradford, Bashford, and Wilson[30] and the studies of Casamajor.[41] In this review of the literature the finding of albumino-cytologic dissociation is reported in about 60 to 80 per cent of cases. Baker states,[42] "The absence of a high total protein may be found in typical cases. The presence of mild or moderate cell increase (in cerebral fluid) chiefly mononuclear cells, is not untenable with this disease (encephalomyelo-radiculitis)." The cerebrospinal fluid dissociation may be a late manifestation. Xanthochromia is present in a small percentage of cases. In 1 case Taylor and McDonald[21] reported a total protein of 49 mg. per cent in the cisternal fluid and 206 mg. per cent in the lumbar spinal fluid. They stated that further detailed study of the "cerebrospinal fluid from the lumbar, cisternal, and ventricular regions should yield results of importance from a diagnostic standpoint." In our review of the literature no such report was found.

Increased intracranial pressure with papilledema has been reported only rarely with this condition.[20] The colloidal gold curve is not charac-

teristic. Sugar and chloride studies are usually within normal limits. One case[43] was reported with temporary spinal cord block of unknown origin.

The blood and urine studies are not significant. A transient leukocytosis is occasionally seen in the early paralytic stage. Anemia is not a constant finding. Baker[10] pointed out that the heterophile antibody test was positive in many successive cases. An elevated blood sedimentation rate has been reported.

Chronaxia and electric stimulation studies have not proved significant.

Clinical Course and Symptomatology

A few authors[8] have pointed out a seasonal incidence of this syndrome. They feel that most cases occur in late summer, autumn, and winter. This is probably only coincidental, since it has not been observed generally. The age and sex incidence are apparently not significant.

In 33 to 55 per cent of cases there is a history of a preceding illness, usually an upper respiratory infection. This illness is often followed by a latent period, which varies considerably from a few days to a few months. The immediate prodromes vary from severe headache, backache, ataxia, to mild paresthesias of the hands and feet. The variants are multiple, and no characteristic onset may be described.

The paresis or paralysis itself is generally symmetrical, equal, and of the flaccid type, although Baker[10, 42] points out that rarely a spastic type is seen. The paresis usually begins in the lower extremities and may spread to the upper extremities. Authors[44, 45, 46] disagree on whether the proximal or the distal groups of muscles are more involved.

The trunk is usually less affected than the limbs, and occasionally the diaphragm is implicated. Tenderness of the muscles or the nerve trunks is noted occasionally. The electric reaction is of degeneration, more frequently incomplete, the changes being most marked in the muscles of the extremities.[47]

The sensory involvement tends to be minimal and of the glove and stocking or acral type of distribution. The deep sensibility tests are neither constant nor characteristic. In general, the deep reflexes are lost, and the superficial reflexes are retained. The anal and vesical sphincters may or may not be involved.

The cranial nerves may be affected, the seventh nerves being those most frequently involved. This paralysis is usually described as peripheral in type.[2] The actual incidence of facial diplegia is problematical, since many authors choose to classify the cases with facial diplegia in a

separate category. A few cases present involvement of the cranial nerves exclusively.[48]

The temperature tends to be normal in most cases. Tachycardia has been described but is at best an inconstant finding.[49]

The status of the patient varies from the completely helpless patient to one with mild peripheral neuritis. The course varies from one of rapid recovery with no residuals to that of a fatal outcome. Often patients make a complete recovery over a period of months. The deep reflexes tend to return slowly.[50] The incidence of contractures is low.[51] Paresis of the facial muscles may persist for years. Relapses or recurrences of the condition are not common.

Fatalities are commonly caused by respiratory or bulbar paralysis, and patients with prolonged courses may die of heart failure[40] or terminal pneumonia.

The prognosis is apparently impossible to predict in any given case and should be guarded. Guillain originally felt that in any case with cerebrospinal fluid dissociation the prognosis was consistently favorable. As previously pointed out, this stand by Guillain was untenable. Mortality varies from 14[52] to 42 per cent.[21] Polan and Baker[53] warned that "a prognosis should be made only after a long period of observation."

Treatment

Guillain[2] injected sodium salicylate intravenously and quinine, methenamine, and colloidal silver intramuscularly. He also introduced colloidal silver by massage. Barker[27] advocated removal of focal infections.

Sahs and Paul[13] employed the Kenny treatment in 8 cases and noted that the treatment did not forestall paralysis in the progressive phase. Gayle *et al.*[54] also used Kenny packs. Vitamins, typhoid shock,[17] x-ray, and arsenicals have also been tried. Recently gratifying results have been reported from the use of neostigmine.[55, 56]

No treatment has been particularly successful. General supportive measures and the use of a respirator in those cases developing respiratory paralysis are the procedures of choice.

Presentation of Cases

During the past nine years 15 typical cases of the Guillain-Barré syndrome have been recognized at Cleveland Clinic. These and 3 other cases are presented because of their clinical similarity and are summarized in the table. Several cases clinically diagnosed as the Guillain-

Case	Age	Sex	Onset	Preceding Infection	Location Initial Symptoms	Cranial Nerve Involvement	Sensory Changes	Deep Reflexes	Cerebrospinal Fluid: Disturbance	Cerebrospinal Fluid: Total Protein mg. per cent	Cerebrospinal Fluid: Cells per cu. mm.	Cerebrospinal Fluid: Xanthochromia	Outcome
1	52	M	April, 1946	0	Cranial nerves	VII	+	Absent	+	105	0	0	Satisfactory improvement in 5 mo.
2	23	F	Mar., 1939	0	Cranial nerves	III, IV, VI VII, VIII	+	Absent	0	455	0	+	Death in 4½ yrs. of terminal pneumonia
3	21	F	July, 1939	0	Arms	0	+	Absent	0	288	0	0	Recovery in 5 mo.
4	23	M	Mar., 1940	+	Legs, arms, cranial nerves	VII	+	Absent	0	240	0	0	Recovery in 5 mo. Residual facial palsy present 6 yrs. later
5	51	M	Sept., 1940	+	Legs and arms	0	+	Absent	0	70	1	0	Recovery in 5 mo.
6	48	M	Feb., 1941	+	Legs and arms	0	+	Absent	0	120	0	0	Recovery in 3 mo. Mild recurrence 4 yrs. later
7	35	F	Feb., 1942	+	Legs and arms	0	+	Absent in legs, diminished in arms	0	65	0	0	Recovery in 11 mo.
8	35	M	April, 1942	0	Legs	0	+	Absent	0	415	0	0	Recovery in 5 mo.
9	56	M	June, 1943	+	Legs and arms	0	+	Absent	0	120	0	0	Recovery in 10 mo.
10	35	F	Feb., 1945	+	Legs and arms	0	+	Diminished	0	120	2	0	Death in 11 mo. of acute necrotizing hepatitis
11	19	F	April, 1945	0	Legs and arms	VII	0	Absent	+	58	1	0	Recovery in 4 mo.
12	54	M	June, 1943	0	Legs and arms	VI(right)	0	Absent	+	385	8	+	Death in 6 mo. of terminal pneumonia
13	21	M	Feb., 1946	0	Legs and arms	0	+	Absent	0	350	0	+	Recovery in 7 mo.
14	52	M	Jan., 1941	0	Legs	0	+	Absent in legs	0	110	0	0	Death in 11 mo. of cardiac failure
15	53	M	Dec., 1937	0	Legs and arms	VII	0	Absent	0	++++ Globulin	0	0	Death in 4 wks. of respiratory failure
16	26	F	May, 1942	Pregnancy	Legs and cranial nerves	VII(left)	+	Absent	0	470	2	+	See analysis of cases
17	51	F	Feb., 1940	Diabetic	Dorsum	0	+	Diminished in legs	0	85	0	0	No improvement in 6 mo.
18	66	F	July, 1940	Diabetic	Legs	0	+	Diminished in legs	0	270	7	0	No follow-up study

Barré syndrome were excluded from this study because of the absence of albumino-cytologic dissociation.

Analysis of Cases

The first 15 cases presented albumino-cytologic dissociation of unknown origin. This group of cases showed the following:

Preceding Infection. Six patients gave a history of an upper respiratory infection, the interval between the infection and onset of symptoms ranging from two weeks to three months.

Age, Sex, and Seasonal Incidence. The age incidence was highest in the sixth decade, in which 6 of the cases occurred. Four cases occurred in the third decade. The sex incidence was 10 in males, 5 in females. The seasonal incidence was highest in February, in which 4 cases had their onset. Three cases originated in April.

Initial Onset. In 9 cases the initial symptoms, mainly of weakness and paresthesias, appeared in the arms and legs. In 2 cases the initial symptoms appeared only in the legs. In 2 cases cranial nerve involvement was the presenting symptom. In 1 case the presenting symptoms were in the arms, and in 1 case the arms, legs, and cranial nerves were first involved.

Cranial Nerve Involvement and Sphincter Disturbances. The cranial nerves were involved in 6 instances. In 4 cases there was bilateral facial diplegia, and in 1 case bilateral facial diplegia was seen in combination with involvement of the third, fourth, sixth, and eighth nerves. This patient had a complete external ophthalmoplegia, an uncommon finding in this syndrome.[10, 24, 57] A right sixth nerve palsy was observed in 1 case. Sphincter disturbances were present in 3 cases, namely urinary retention in 2 instances and fecal incontinence in the third.

Temperature and Pulse. The temperature in all cases was within normal limits, and the pulse rate was over 100 in 6 cases.

Motor and Sensory Involvement. The most common finding was motor weakness of the legs. Sensory involvement was most common in the legs, chiefly of the glove and stocking type of acro-anesthesia. In 3 instances no sensory loss was noted. In 2 cases the sensory loss was confined to the ulnar distribution of the hands. Vibratory sense and position sense were diminished in the legs in 6 instances. The nerve trunks were tender in 1 case. In only 1 instance was respiratory failure observed in the acute phase.

Reflexes. The deep reflexes were absent in 12 patients. In 1 the deep reflexes were absent in the legs only, in another they were absent in the legs and diminished in the arms, and in a third patient all deep

reflexes were diminished. In most instances the abdominal reflexes were preserved.

Laboratory Study. Hemoglobin was below 70 per cent in only 1 instance. The highest leukocyte count observed was 11,950 per cu. mm. Small amounts of albumin were found in the urine in 4 cases. The cerebrospinal fluids varied from a total protein of 58 mg. per cent to 455 mg. per cent. The cell counts varied from 0 to 8 cells per cu. mm. Xanthochromia was observed in 3 cases. The colloidal gold curve studies were not significant. The Wassermann reactions were negative in the spinal fluid and blood in every case. Cerebrospinal fluid studies were normal when case 11 was admitted to Cleveland Clinic Hospital on April 17, 1945, nine days after the onset of initial symptoms. Nine days later the cerebrospinal fluid presented a total protein of 58 mg. per cent and 1 cell per cu. mm. Subsequently this patient was followed at Henry Ford Hospital in Detroit, and the cerebrospinal fluid studied there in June, 1945, revealed a total protein of 425 mg. per cent and 1 cell per cu. mm. It has been previously noted that cerebrospinal protein may not be elevated early in this syndrome.

Treatment

Various forms of therapy were used, including deep x-ray over the dorsal region of the spine, typhoid shock, and arsenical therapy. Vitamins, chiefly B complex, and liver extract were also administered. Therapy had little if any effect on the clinical course.

Results

Five of the cases terminated fatally. One patient died of respiratory failure four weeks after the onset of initial symptoms; 1 died of terminal pneumonia after six months without improvement; 1 died of cardiac failure after nine months of continuous illness; 1 died of necrotizing hepatitis after eleven months. The fifth patient lingered on for almost five years without improvement and then succumbed to terminal pneumonia. The ages of these patients were 54, 53, 52, 35, and 23, respectively. The sex incidence was 3 males and 2 females. In only 1 case was a previous history of infection elicited. Xanthochromia of the cerebrospinal fluid was present in 2 of the fatal cases.

In 7 cases there was complete recovery in from three to ten months except for absent tendon reflexes in 2 instances. One patient was improving satisfactorily five months after onset of initial symptoms. The only residual was slight facial palsy (still present six years later) in 1 case and slight weakness of the legs in a second case. In case 6 a mild recur-

rence of the original symptoms occurred four years after the original illness but cleared up completely in a few months.

Necropsy Study. The necropsy study of case 10 is included through the cooperation of Dr. H. K. Giffen of Youngstown, Ohio. The significant findings were: (1) focal degeneration in and around the spinal cord; (2) edema of the brain with hyperemia; (3) degeneration of peripheral nerves; (4) focal degeneration of striated muscle; and (5) marked central and midzone degeneration of the liver. (This was similar to liver changes previously described by Aring.[58])

Through the courtesy of Dr. A. Theodore Steegmann, Kansas City, Missouri, the necropsy study of the spinal cord in case 14 is presented. His pathologic diagnoses were (1) degeneration of the peripheral nerves and (2) vacuolization of the cytoplasm of the anterior horn cells.

Permission for necropsy was not obtained in the remaining fatal cases.

Additional Cases. Case 16 is included in this paper because it presents a picture identical with that of the Guillain-Barré syndrome associated with pregnancy[33,59] and because the subsequent development of papilledema was unusual.[20,60] This patient entered Cleveland Clinic in October, 1942, thirteen days after she had been delivered of normal healthy twins. In the first three months of pregnancy she had severe hyperemesis which resulted in a loss of 25 pounds. In the fourth month she developed a left facial palsy which lasted ten days. After the fourth month she noted weakness in her legs accompanied by numbness and soreness. The weakness progressed until the patient was unable to walk at term and was accompanied by tingling, stiffness and mild clumsiness of the hands. Examination revealed loss of all deep reflexes and diminished sensation from the hips distally. Lumbar puncture revealed an initial pressure of 250 mm. of water with normal dynamics and xanthochromic fluid containing a total protein level of 470 mg. per cent and 2 cells per cu. mm. A tentative diagnosis of the Guillain-Barré syndrome was made, and at the time of discharge, supportive therapy only was prescribed. This same patient was admitted to Johns Hopkins Hospital in Baltimore in January, 1943, unimproved, at which time she had bilateral papilledema and a cerebrospinal fluid pressure of over 600 mm. of water. Total protein was 420 mg. per cent. An air injection was done and the ventricles were found to be normal. A right subtemporal decompression was carried out. At last report the patient had shown no improvement. This case was previously reported by Ford and Walsh.[60]

Cases 18 and 19 are presented here as examples of the clinically identical picture seen in diabetes mellitus.

Conclusion

From the foregoing discussion it is evident that a syndrome exists which is of unknown cause, is characterized by polyneuritis, is often accompanied by facial diplegia, usually presents albumino-cytologic dissociation of the cerebrospinal fluid, and has a favorable prognosis in the majority of cases.

This syndrome is seen both as a primary condition and as one associated with other conditions, such as syphilis, diphtheria, serum sickness, fever therapy, pregnancy, and reaction after exposure to mustard gas. The precise nature is obscure in both the primary and associated forms. No recognized factors in any case of diphtheria, diabetes, syphilis, and the like precede or prognosticate the development of this syndrome.

For the sake of clarification of terminology and out of deference to the men who first pointed out albumino-cytologic dissociation in association with polyneuritis, it is suggested that all cases of the aforementioned type, whether of the primary or of the associated variety, be grouped under the title of the Guillain-Barré syndrome pending the time when the precise nature and etiology of this complex are understood.

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