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Acute axonal idiopathic polyneuropathy: a Guillain-Barré syndrome variant?

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We report 7 cases of acute polyneuropathy fitting the NINDS diagnostic criteria for GBS. Electrophysiological study and sural nerve biopsy revealed a picture of axonal polyneuropathy, without changes suggesting demyelination. We discuss whether the acute idiopathic axonal neuropathy belongs to the GBS spectrum or represents a separate clinico-pathological entity.

Key Words: Guillain-Barré syndrome — polyneuropathy — axonal degeneration

Introduction

Guillain-Barré syndrome (GBS) is a clinically defined entity, which has no independent laboratory marker for diagnosis. The diagnostic criteria of the NINDS [3], reaffirmed at the last Symposium on GBS [4], are widely accepted. Only clinical features are required. Cerebrospinal fluid and electrodiagnostic features support the diagnosis, but are not necessary for it, and cannot exclude it. Pathological aspects are not mentioned. However, in the majority of GBS patients, electrodiagnostic and pathological studies reveal a picture of multifocal demyelinating polyneuropathy with occasional axonal degeneration [2, 5]. The disease, also named acute inflammatory demyelinating polyradiculoneuropathy (AIDP), is traditionally considered to be the consequence of an immune-mediated process directed against myelin components [17]. Axonal degeneration may be secondary, due to a "bystander effect" [13]. Nevertheless, a few patients show evidence of axonal loss alone [1, 8, 15].

We report 7 cases of acute polyneuropatPhy that fulfil the clinical criteria for the diagnosis of GBS [3], but show electrophysiological and pathological (in 2 cases with nerve biopsy) features of axonal degeneration, in the absence of demyelinating changes.

Patients and methods

The 7 patients in this study were identified over a 5-year period (1985-1990) among the patients admitted to the Neurological Department and Intensive Care Unit of the Catholic University of Rome. *Motor conduction studies* were performed using the standard technique of supramaximal percutaneous stimulation and surface electrode recording. Compound muscle action potential (CMAP) amplitudes were measured peak to peak and were evaluated for stimulation at distal (wrist, ankle) and proximal (axilla, popliteal fossa) sites. 21 nerves were examined, (mean, 2.7 per patient; range 2-5). *Sensory conduction studies* were also performed with conventional surface techniques, orthodromically. Sensory action potential (SAP) amplitudes were measured peak to peak. 23 nerves were examined, range 2-4 per patient. *Needle electromyography recordings* were performed using standard concentric needle electrodes. At *nerve biopsy* in cases 1 and 5, a sural nerve sample was fixed in glutaraldehyde 2.5%, post-fixed in osmium tetroxide 1%, processed and embedded in Spurr resin. Semi-thin sections were stained with toluidine blue. Thin sections were stained with uranyl acetate and lead citrate prior to examination using Philips 400 EM. 60 single fibers were teased in each patient and classified according to

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TABLE I. *Clinical features.*

Case	Antecedent event	T1 (days)	Peak severity	Clinical findings	T2 (days)	T3 (months)	PE (sessions)
1 58 yrs female	sciatica	9	respiratory failure	tetraplegia IX XII c.n. distal hypoesthesia areflexia	35	24	5
2 77 yrs male	fever	2	respiratory failure	severe tetraparesis IX c.n. areflexia	120	6	3
3 73 yrs female	—	12	lost deambulation	severe tetraparesis areflexia	25	5	3
4 43 yrs female	sciatica	5	lost deambulation	severe tetraparesis areflexia	21	4	0
5 62 yrs male	—	28	lost deambulation	severe paraparesis lower limbs areflexia	21	4	0
6 64 yrs female	myalgia	21	lost deambulation	severe tetraparesis lower limbs areflexia distal hypoesthesia	35	24	0
7 43 yrs female	—	7	death	tetraplegia areflexia distal hypoesthesia	—	—	3

T1 — period of deterioration
T2 — plateau
T3 — time to recovery of independent deambulation

Dyck, 1975 [7]. Another part of the sample was frozen and stained with hematoxylin-eosin.

Results

Clinical features. Table I gives the clinical data. There were 2 males and 5 females, aged 43 to 77 years (mean, 60 years). No patient had clinical evidence or history of abnormal porphyrin metabolism, bexacarbon abuse, diphtheria or HIV infection, poliomyelitis, botulism, lead exposure, diabetes, malignancies, or other chronic diseases. In the month preceding the onset one patient experienced an upper respiratory tract infection with fever, two had low back pain and sciatica, and one had complained of diffuse persistent myalgias.

The onset consisted of paresthesia and/or limb weakness. The period of deterioration (T1) ranged from 2 to 28 days (mean, 12 days), and at the peak neurological impairment was severe: all patients lost walking, 3 required mechanical ventilation, and one of these died. Examination at peak revealed tetraplegia or severe tetraparesis in each patient, except case 5 with only mild weakness in the upper limbs. Tendon jerks were unobtainable in all but two patients: cases 5 and 6 had hypoactive proximal reflexes in the upper limbs. In two cases cranial nerves were involved, and one patient showed glove-stocking hypoesthesia. 4 patients were treated with a course of plasma-exchange (3-5 sessions with 60% of the total plasma exchanged per session and replacement with 4% albumin solution).

The start of improvement was gradual and difficult to establish. The plateau (T2) ranged from 14 to 120 days (mean, 42 days); it was particularly prolonged (120 days) in case 2, a 77 year old man who had infectious complications. In the other patients T2 was 14-35 days. All the surviving pa-

TABLE II. *Cerebrospinal fluid findings.*

Case	Time (days from onset)	Proteins mg/dl (n.v. 20-40)	Cells cells/ml	IgG/albumin ratio n.v.<15%
1	2 5	78 100	18 15	—
2	64	146	15	13.6%
3	13	77	2	10.5%
4	15	119	3	—
5	18 29	39 38	0 0	29%
6	5	113	4	20%
7	35	56	0	—

tients improved. The time necessary to recover independent walking (T3) ranged from 4 to 24 months (mean 11). Residual deficits, after a follow-up time of 5 to 60 months, are present in all but one case (n. 5, the least severe).

Laboratory data. Routine analysis and immunoelectrophoresis were normal in all patients. Cerebrospinal fluid (CSF) examination (Table II) revealed an increased content of protein in six patients. In case 5 CSF protein content was at the upper limit of normal in two samples (at weeks 3 and 5 of the disease). Cells were absent or fewer than 4/ml (mononuclear leukocytes) in 5 cases. There were 18 (15 in a second sample after 2 days) in case 1, and 15 in case 2. The IgG/albumin ratio was performed in 4 patients (CSF of cases 1, 4 and 7 had been examined in other hospitals before admission to ours): in cases 5 and 6 it was high (29 and 20%).

Electrophysiological study (Table III). EMG examination after the first month of disease showed denervation signs (fibrillation and positive sharp wave potentials) in all cases. Voluntary effort was characterized by reduced number of motor unit potentials with high discharge frequency. The most evident result in motor conduction studies was a marked reduction in the amplitude of CMAP evoked by distal stimulation. It was normal only in the ulnar nerve of case 5 (who showed only slight involvement of the upper limbs). With this exception, the mean amplitude of distal CMAP was between 0 and 28.5% of the lower normal limit. There was no significant variation in amplitude between distally and proximally evoked CMAP. Motor conduction velocities and distal latencies were always normal when CMAP was detectable. SAPs were absent or markedly reduced in all nerves in case 1. Case 2 showed a mild reduction of SAP of the ulnar nerve. Sensory conduction velocities were normal in all patients.

Nerve biopsy findings. Sural nerve biopsy was carried out in patients 1 and 5. In case 1 it was performed in the third week of the disease. Semithin transverse sections (Fig. 1) showed a large number of degenerating axons. Hematoxylin-eosin stained frozen transverse sections revealed no inflammatory infiltrate or vascular change. Examination of teased single fibers failed to show any demyelination (category C and D, Dyck 1975) [7], whereas 65% of fibers showed axonal degeneration (category E). In case 5 the nerve biopsy was performed in the ninth week of the disease. Semi-thin sections (Fig. 2) showed a slight reduction in the density of myelinated fibers, and axonal degeneration. Hematoxylin-eosin stained sections revealed no inflammatory infiltrates. Teased single fibers showed no demyelination (C and D); 31% of fibers were degenerating (E), and 6% showed remyelination (F). In both patients the electron microscope examination revealed ongoing axonal degeneration but no demyelinating changes.

Discussion

We report 7 cases which meet the NINDS clinical criteria for GBS [3]. CSF examination supported this diagnosis with albumin-cytological dissociation, in 4 cases, and classified as variants cases 1 and 2 (CSF mononuclear leukocytes more than 10 but less than 50) and case 5 (CSF protein within normal range after 5 weeks).
The nerve conduction study showed normal velocities and absence of conduction blocks. The

TABLE III. *Nerve conduction.*

Nerve	Motor					Sensory	
	dCMAP mv	pCMAP mv	%CMAP LLN-mean	DL msec	MCV m/sec	SAP uv	SCV m/sec
Case 1			1.9				
ulnar	0.2	0.2		3	59	0	—
median	0.2	0.2		3.4	56	0.7	51
tibial	2.1	2		3	44		
sural						3	62
radial						0.7	47
Case 2			23.5				
ulnar	1.2	1.2		2.6	54	3	48
peroneal	1.5	1.5		4.2	44		
sural-r						8	52
sural-l						17	51
radial						5	45
Case 3			16.7				
ulnar	1.5	1.5		2.2	46	11	48
median	2	2		3.4	48	11	46
peroneal	0.6	0.6		4	47		
sural						30	44
Case 4			24.4				
ulnar	1.5	1.2		2.6	54	8	47
median-r	5.8	5.5		3.8	57	11	55
median-l	2.8	2		3.8	53		
peroneal-r	0.1	0		6.4	—		
peroneal-l	0.3	0.3		5.8	45		
sural						8	46
radial						13	51
Case 5			4% lower limbs 242% upper limbs				
ulnar	20	17		2.6	51	6	52
peroneal	0.2	0.2		4.6	44		
radial						8	55
sural-r						9	48
sural-l						13	47
Case 6			28.5%				
ulnar	0.4	0.4		3.1	55	5	55
median	0.6	0.5		3.2	47		43
sural						10.5	
Case 7			0				
ulnar	0	0		—	—	8	58
median	0.2	0		3.9	—	8	53
Normal range							
ulnar	7-31			2 -3.1	47-63	4 -40	46-65
median	7-25			2.6-4.1	47-55	5 -70	42-62
peroneal	5-15			3.4-6.5	43-50		
sural						3.5-25	44-58

dCMAP: distal compound motor action potential
pCMAP: proximal compound motor action potential
%CMAP LLN-mean: mean percentage of the lower limit of normal
DL: distal latency
MCV: motor conduction velocity
SAP: sensory action potential
SCV: sensory conduction velocity.

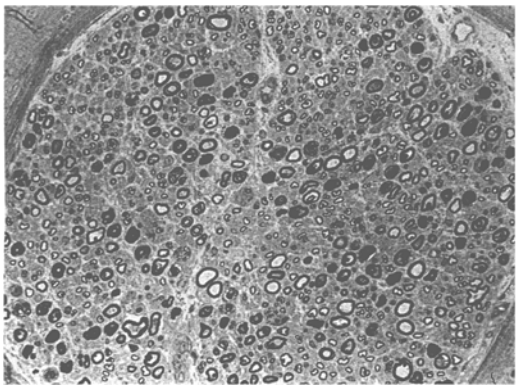

Fig. 1. *1 um-thick tranverse section of sural nerve biopsy of Case 1 showing degenerating axons. Toluidine blue stain. X 1625.*

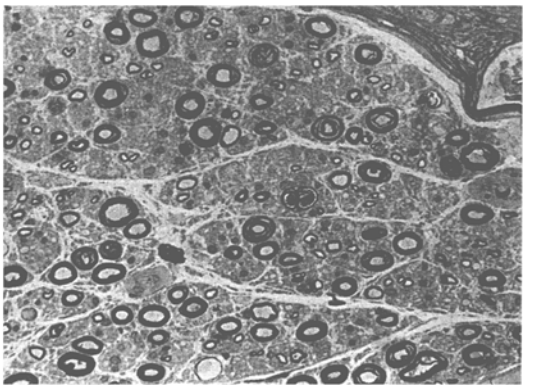

Fig. 2. *1 um-thick transverse section of sural nerve biopsy of Case 5 showing mild reduction in the density of myelinated fibers, and axonal degeneration. Toluidine blue stain. X 2031.*

major common feature is a marked reduction in the amplitude of the motor response evoked by distal stimulation. On the basis of other electrophysiological, pathological and clinical features, we consider this finding to be an expression of axonal degeneration rather than of distal demyelination. These features are:
1) normal distal latency
2) no further reduction in amplitude following proximal stimulation
3) normal conduction velocity
4) evidence of axonal degeneration without demyelination in the sural nerve biopsies
5) slowness of recovery, compatible with nerve regeneration.
Known etiologies for acute polyneuropathies (infectious, toxic, paraneoplastic, diabetic, secondary to other chronic diseases) were excluded.
Albers et al. [1] reported two cases of GBS with electrophysiological evidence of axonal degeneration alone. The clinical severity was not specified.
Feasby et al. [8] described 5 cases of severe GBS, with electrically unexcitable motor nerves. Postmortem examination of multiple roots and distal nerves, performed in one patient, showed severe axonal degeneration, with no inflammation or demyelination.
Other authors [5, 6, 11, 12, 14, 15, 16] reported some cases of GBS with exclusive or predominant evidence of axonal damage: they are usually severe cases, with rapid deterioration and poor prognosis.
Hartung et al. [9], on the basis of experimental studies, proposed that the profound axonal degeneration observed in this "hyperacute form" of GBS may follow an autoimmune reaction against a myelin antigen, not necessarily implying any other antigen or etiology. In adoptive transfer-experimental allergic neuritis (AT-EAN), the injection in rats of a high cell dosage of myelin protein P2-specific T lymphocytes produces fulminating axonal neuritis, whereas smaller numbers of cells give rise to a mild demyelinating neuropathy [10]. In EAN the injection of myelin in rats produces a demyelinating allergic neuropathy, but larger doses of immunogen lead to significant axonal damage, together with more extensive demyelination.
The pathogenetic mechanism of acute idiopathic polyradiculoneuropathy with electrophysiological and morphological evidence of axonal degeneration but without demyelination is still a matter of debate. It is unclear at present whether the axonal form belongs to the GBS spectrum or represents a separate disease. In our opinion three hypotheses are possible to explain these cases:
1) primary demyelinating disease (GBS) in which the immune reaction is so intense that entire nerve fibers are destroyed [9]
2) primary axonal disimmune disease
3) primary axonal non-inflammatory disease.
Hartung's hypothesis could explain the majority of our cases of "pure axonal GBS": these are severe with rapid worsening, and the intensity of the immune reaction could led to axonal destruction as a "bystander effect" [13]. Furthermore, conduction blocks could be present in the proximal nerve segments (between roots and axilla or popliteal fossa), which were not explored in our study.
However, this explanation can hardly be applied to patient 5, in whom clinical features seems to exclude a very intense immune reaction. The fol-

lowing features differentiate this case from the others reported both here and elsewhere: 1) the worsening time was longer (28 days); 2) peak deficits were much less severe: the patient had lost walking but the upper limbs were involved only mildly; 3) recovery, although requiring a long time, was complete.
In the other reported case of "axonal GBS" with pathological data [8], as in ours, inflammatory infiltrates were not observed. This does not rule out an inflammatory disimmune origin of the disease, since in GBS the lesions are scattered, and not infrequently sural nerve biopsy fails to show inflammation. Furthermore, in case 5 the IgG/albumin ratio was raised, supporting the hypothesis of a disimmune mechanism. However, until histopathological or experimental proof can be offered for the inflammatory disimmune origin of the process, we can not exclude the possibility of a different pathogenesis.

Sommario

Descriviamo 7 casi di polineuropatia acuta che soddisfano i criteri diagnostici del NINDS (3). Lo studio elettrofisiologico e la biopsia di nervo surale (eseguita in due pazienti) hanno evidenziato un quadro di neuropatia con evidenti fenomeni di degenerazione assonale, ma senza segni di demielinizzazione. Discutiamo se la neuropatia acuta assonale idiopatica appartiene allo spettro della sindrome di Guillain-Barré o costituisce una diversa entità clinico-patologica.

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References

[1] ALBERS J.W., DONOFRIO P.D., MCGONAGLE T.K.: *Sequential electrodiagnostic abnormalities in acute inflammatory demyelinating polyradiculoneuropathy.* Muscle nerve 8:528-539, 1985.

[2] ASBURY A.K., ARNASON B.G., ADAMS R.D.: *The inflammatory lesion in idiopathic polyneuritis.* Medicine 48:173, 1969.

[3] ASBURY A.K., ARNASON B.G., KARP H.R., MCFARLIN D.E.: *Criteria for diagnosis of Guillain-Barré syndrome.* Ann. Neurol. 3:565-566, 1978.

[4] ASBURY A.K., CORNBLATH D.R.: *Assessment of current diagnostic criteria for Guillain-Barré syndrome.* Ann. Neurol. 27 (Suppl.):21-24, 1990.

[5] BROWN W.F., FEASBY T.E.: *Conduction block and denervation in Guillain-Barré polyneuropathy.* Brain 107:219-239, 1984.

[6] CORNBLATH D.R., MELLITS E.D., GRIFFIN J.W., MCKAHN G.M. et al. *and the* Guillain-Barré Study Group: *Guillain-Barré Study Group: Motor conduction studies in Guillain-Barré syndrome: description and prognostic value.* Ann. Neurol. 23:354-359, 1988.

[7] DYCK P.J.: *Pathologic alterations of the peripheral nervous system in man.* In: Peripheral Neuropathy. Dyck P.J., Thomas P.K., Lambert E.D. editors. W.B. Saunders Co., Philadelphia, 1975.

[8] FEASBY T.E., GILBERT J.J., BROWN W.F., BOLTON C.F., et al.: *An acute axonal form of Guillain-Barré-polyneuropathy.* Brain 109:1115-1126, 1986.

[9] HARTUNG H.P., HEININGER K., SCHAEFER B., FIERZ W., TOYKA K.V.: *Immune mechanisms in inflammatory polyneuropathy.* Ann. N. Y. Acad. Sci. 540:122-161, 1988a.

[10] HEININGER K., STOLL G., LININGTON C., TOYKA K.W., WEKERLE H.: *Conduction failure and nerve conduction slowing in experimental allergic neuritis induced by P2-specific T-cell lines.* Ann. Neurol. 19:44-49, 1986.

[11] KANDA T., HAYASHI H., TANABE H., TSUBAKI T., ODA M.: *A fulminant case of Guillain-Barré syndrome: topographic and fiber size related analysis of demyelinating changes.* J. Neurol. Neurosurg. Psy. 52:857-864, 1989.

[12] LOEFFEL N.B., ROSSI L.N., MUMENTHALER M., LUETSCHG J., LUDIN H.P.: *The Landry-Guillain-Barré syndrome.* J. Neurol. Sci. 33:71-79, 1977.

[13] MADRID R.E., WISNIOWSKI H.M.: *Axonal degeneration in demyelinating disorders.* J. Neurocytol. 6:103-117, 1977.

[14] MCKAHN G.M., GRIFFIN J.W., CORNBLATH D.R., MELLITS E.D. et al. and The Guillain-Barré Study Group: *Plasmapheresis and Guillain-Barré syndrome: analysis of prognostic factors and the effect of plasmapheresis.* Ann. Neurol. 23:347-353, 1988.

[15] MILLER R.G., PETERSON C., ROSEMBERG N.L.: *Electrophysiologic evidence of severe distal nerve pathology in the Guillain-Barré syndrome.* Muscle Nerve 10:524-529, 1987.

[16] ROPPER A.H.: *Severe acute Guillain-Barré syndrome.* Neurol. 36:429-432, 1986.

[17] TOYKA K.V., HARTUNG H.P.: *Immune mechanisms and therapeutic approaches in inflammatory disorders of the peripheral nervous system.* Ital. J. Neurol. Sci. 1 (suppl.):11-17, 1991.