

CHRONIC RECURRENT GUILLAIN-BARRÉ SYNDROME

REPORT OF 3 CASES

ANTÔNIO RODRIGUES DE MELLO * — MARCOS R. G. DE FREITAS **
LEILA CHIMELLI ***

SUMMARY — The classical Guillain-Barré syndrome is an acute or subacute polyradiculoneuropathy whose main clinical features are progressive weakness of the limbs, decrease or absence of tendon reflexes, and sensory changes. Although in most of the cases there is complete recovery in weeks or months, some patients have a slow and progressive relapsing course and present thickening of the peripheral nerves. In this paper we describe three cases of the chronic and relapsing variety of Guillain-Barré syndrome, two of which had prominent hypertrophic changes in the peripheral nerves with onion bulb formations. The clinical and pathological features of this disease are reviewed. The three patients improved with the use of steroids.

Síndrome de Guillain-Barré crônica recorrente: registro de 3 casos.

RESUMO -- A síndrome de Guillain-Barré clássica é polirradiculoneuropatia aguda ou sub-aguda, cujos principais aspectos clínicos são: fraqueza progressiva dos membros, redução ou ausência de reflexos tendinosos e alterações sensitivas. Embora na maioria dos casos haja recuperação completa em semanas ou meses, em alguns pacientes o curso é lento, progressivo ou recidivante e há espessamento dos nervos periféricos. No presente artigo descrevemos três casos da variedade crônica e recidivante da síndrome de Guillain-Barré, dois dos quais tinham alterações hipertróficas proeminentes nos nervos periféricos com formações em bulbo de cebola. Os aspectos clínicos e patológicos desta doença são revistos. Os três pacientes melhoraram com o uso de esteróides.

The Guillain-Barré (GB) syndrome is a polyradiculoneuropathy whose main clinical features are progressive weakness of the limbs, decrease or absence of tendon reflexes, sensory changes and, less frequently, cranial nerve involvement². The cerebrospinal fluid (CSF) shows albuminous-cytologic dissociation, and there is electrophysiological evidence of slow nerve conduction. In the peripheral nervous system the main pathological finding is demyelination^{2,20}. While in most patients the illness is acute or sub-acute with complete recovery in weeks or months, some cases have a slow and progressive relapsing course, and present thickening of the peripheral nerves^{2,8,9}. In spite of the clinical presentation and the variety of names given by various authors^{9,21} to the latter forms, they share with the classical GB syndrome electrophysiological, humoral and pathological findings.

In the present paper three cases of the chronic and relapsing variety of GB syndrome are described, which are also unusual for some morphological findings in the peripheral nerves.

Trabalho das Disciplinas de Neurologia e de Neuropatologia, Faculdade de Medicina, Universidade Federal Fluminense: * Professor Emérito da UNIRIO; ** Professor Adjunto de Neurologia; *** Professor Adjunto de Neuropatologia.

CASE REPORTS

Case 1 — LWM, a 12-year-old girl, presented in June 1958 weakness and paraesthesia of all 4 limbs starting in the lower limbs which progressed rapidly. She denies any toxic or alcoholic ingestion and there is no similar case in the family. Neurological examination showed tetraparesis, reduced tendon reflexes, and slight distal superficial hypoesthesia in arms and legs; cranial nerves were normal. CSF examination showed 14 cells/mm³, proteins 138 mg/dl. Routine blood tests were normal. She recovered completely after 30 days. In 1972 at the age of 26 she had a recurrence. There was generalized deep areflexia, superficial hypoesthesia in the lateral aspect of the feet. The cubital nerves were thickened and the brachial plexus was palpable and visible on both sides. Electromyographic findings suggested a peripheral nerve disorder. She improved again but in 1974 she had a new recurrence which improved with dexamethasone. Three months later, after the steroid had been discontinued there was a new recurrence with unilateral peripheral facial palsy. There were three other recurrences in June and December 1975 and in December 1981, following reduction of the steroid dose. The CSF examination in 1981 showed 1.7 cells/mm³, 216 mg/dl protein, and 16% of gamma globulin. At this occasion the biopsy of a supraclavicular mass showed an enlarged nerve, which was examined histologically. The specimen consisted of a thick nerve which was processed for paraffin embedding. Longitudinal sections stained with haematoxylin and eosin (HE) showed extremely large nerve fibres surrounded by numerous Schwann cell nuclei. On transverse sections it showed concentric proliferation of Schwann cells with the appearance of onion bulbs (Fig. 1a). Lymphocytes, mainly around blood vessels were also seen (Fig. 1b). The appearances were those of a hypertrophic chronic inflammatory neuropathy. The patient died soon after last recurrence with cardio-respiratory failure. Postmortem examination was not performed.

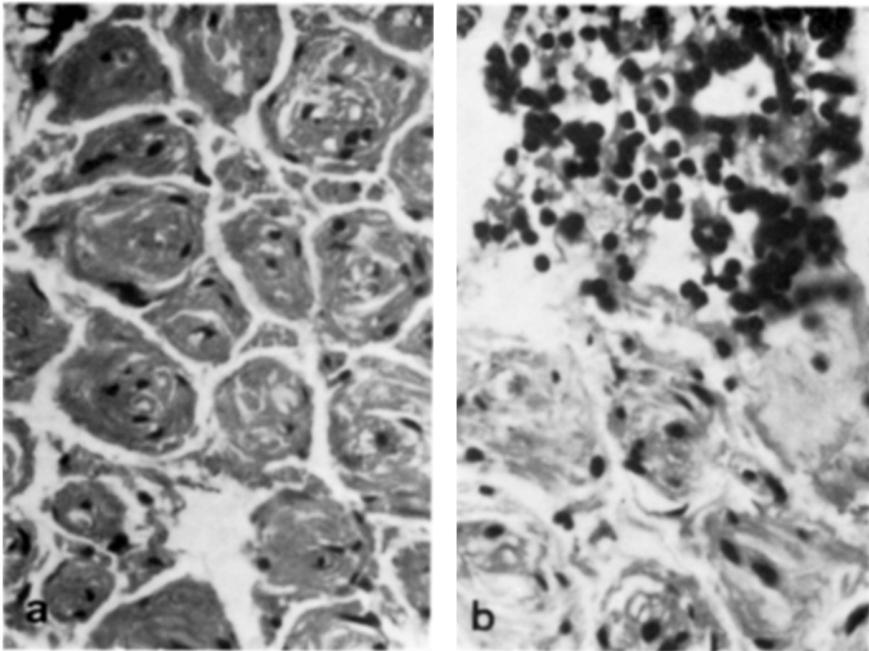


Fig. 1 — a. Paraffin section of the nerve from case 1 showing concentric proliferation of Schwann cell cytoplasm with the appearance of onion bulbs. b. Another area from the same nerve showing a cluster of lymphocytes around a vessel (HE $\times 400$).

Case 2 — OA, a 52-year-old black female was seen in April 1986. Symptoms had started in 1981 with paraesthesiae in hands and feet followed by limb weakness with difficulty in walking. She improved considerably on prednisone. Since then and for about 6 years she presented similar episodes, usually preceded by a cold. With the steroid therapy there was

partial remission of the weakness, and between the relapses she experienced only little difficulty in walking. There is no history of toxic or alcoholic ingestion and no diabetes. No similar cases occurred in the family. Neurological examination — Coarse postural tremor in hands, ataxic type of gait with support. Tetraparesis predominantly distal and more marked in lower limbs, generalized hypotonia, proprioceptive ataxia of all limbs, superficial and deep hypoesthesia in lower limbs. Cranial nerves normal. Peripheral nerves palpable but not thickened. CSF examination — In January 1983: 0 cells/mm³, proteins 150mg/dl; in May 1986: 28 cells/mm³ (60% polymorphs and 40% mononuclear), proteins 325mg/dl. Routine blood and urine tests were normal. Electroneuromyography showed severe involvement of distal neuroconduction. Sural nerve biopsy — A segment of nerve, 2 cm in length was fixed partly in 10% formalin for paraffin embedding and partly in 3% glutaraldehyde in 0.05 M Na cacodylate buffer for Araldite embedding and for teasing. Paraffin sections stained with HE showed apparently normal nerve fibres with some increase in number of Schwann cells. No inflammatory cells were seen. One micron thick Araldite sections stained with toluidine blue showed some clusters of small myelinated axons inside single Schwann cells indicating regeneration. Some concentric proliferation of Schwann cell cytoplasm surrounding myelinated fibres with thin myelin sheath were also seen (Fig. 2). This was

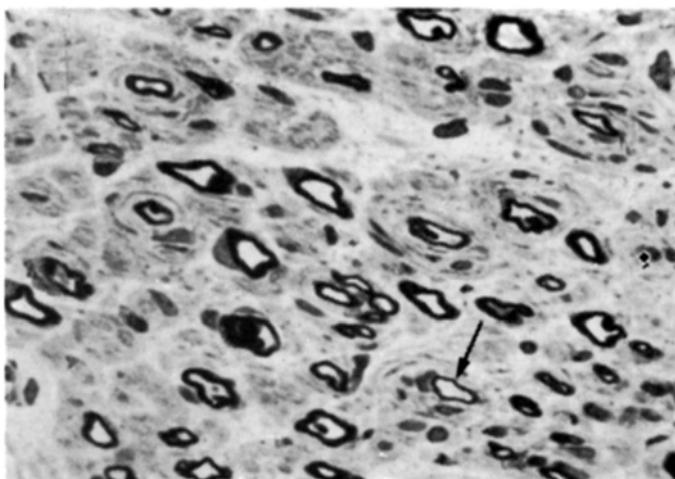


Fig. 2 — One micron Araldite section of the nerve from case 2 showing concentric proliferation of Schwann cell cytoplasm around myelinated fibres, one of which (arrow) has a thin myelin sheath (Toluidin blue $\times 400$).

confirmed in thin sections where some Schwann cells devoid of axons (Fig. 3a) and naked axons (Fig. 3b) could be observed. Only few unmyelinated fibres were present. Single teased fibres showed segmental demyelination and a great variation of internodal length. The features were suggestive of a chronic demyelinating neuropathy with signs of remyelination, axonal regeneration and beginning of onion bulb formation. With prednisone, even after reduction of the dose, significant improvement was obtained and she was able to walk without support.

Case 3 — MVC, a 67-year-old white female was seen in November 1936. In 1981 she presented cervical pain irradiating to the left arm (like a shock), when she was submitted to myelography and surgery of the cervical spine with temporary improvement. In 1983 she had a low back pain radiating to posterior surface of right thigh and weakness of this limb. A laminectomy was performed with some relief of the pain for a limited period. This was followed by weakness of all limbs, asymmetric, with difficulty in walking. The pain was mainly in the left limbs. Some relief was obtained with carbamazepine and chlorimipramine. There is no history of toxin, alcoholism or diabetes. No similar cases in the family are reported. Neurological examination showed distal amyotrophy in all 4 limbs with slight deformity of the left hand, pes equinus, bilateral steppage gait (with support), distal tetraparesis more severe in the lower limbs generalized hypotonia, bilateral Babinski

sign; left bicipital reflexes were present, other tendinous reflexes were absent; superficial hypoesthesia below the knees and the wrists, loss of vibratory sense in lower limbs. Cranial nerves were normal. Cubital nerves were uniformly palpable and thick (more on the left). Right posterior auricular nerve was thick. CSF examination showed 1 cell/mm³, total proteins 48mg/dl, IgG 5.6mg%. Electroneuromyography showed a great reduction in sensitive and motor nerve conduction in all 4 limbs. Sural nerve biopsy — A two cm nerve was fixed and processed as described in case 2. Paraffin sections stained with HE showed thick nerve fibres, increase in number of Schwann cell nuclei and no inflammatory cells. One micron

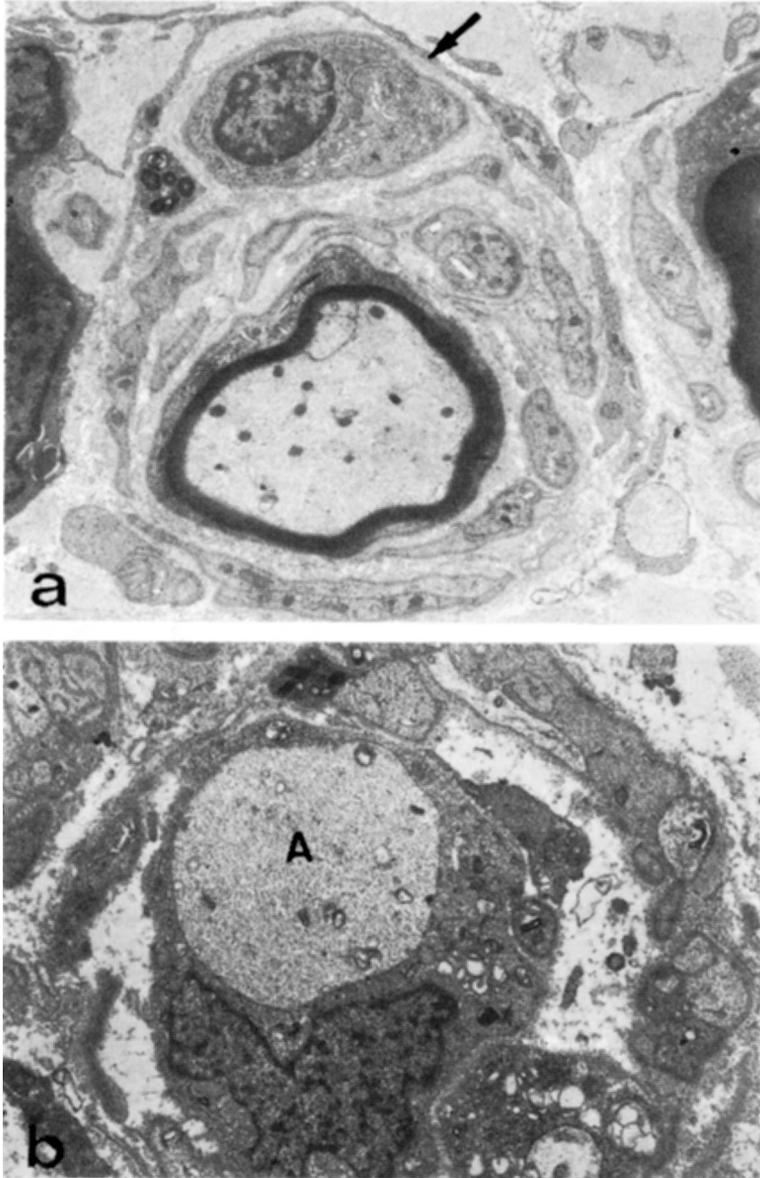


Fig. 3 — a. Electronmicrograph of the nerve from case 2 showing abundant Schwann cell cytoplasm around a myelinated fibre, and a Schwann cell devoid of axon (arrow). b. Electronmicrograph of the nerve from case 2 showing a demyelinated axon (A) surrounded by the Schwann cell (×3000).

transverse Araldite sections stained with toluidine blue showed that almost all the fibres were surrounded by Schwann cell cytoplasm concentrically proliferated with the appearance of onion bulbs (Fig. 4a). Clusters of regenerated axons were seen as well as thinly myelinated axons indicating remyelination. Ultrathin sections examined with the electron microscope showed similar features (Fig. 4b) which were those of a hypertrophic type of chronic neuropathy. The patient was put on 60mg prednisone per day, and 30 days after she could walk without support with great improvement of the strenght and sensation in all 4 limbs.

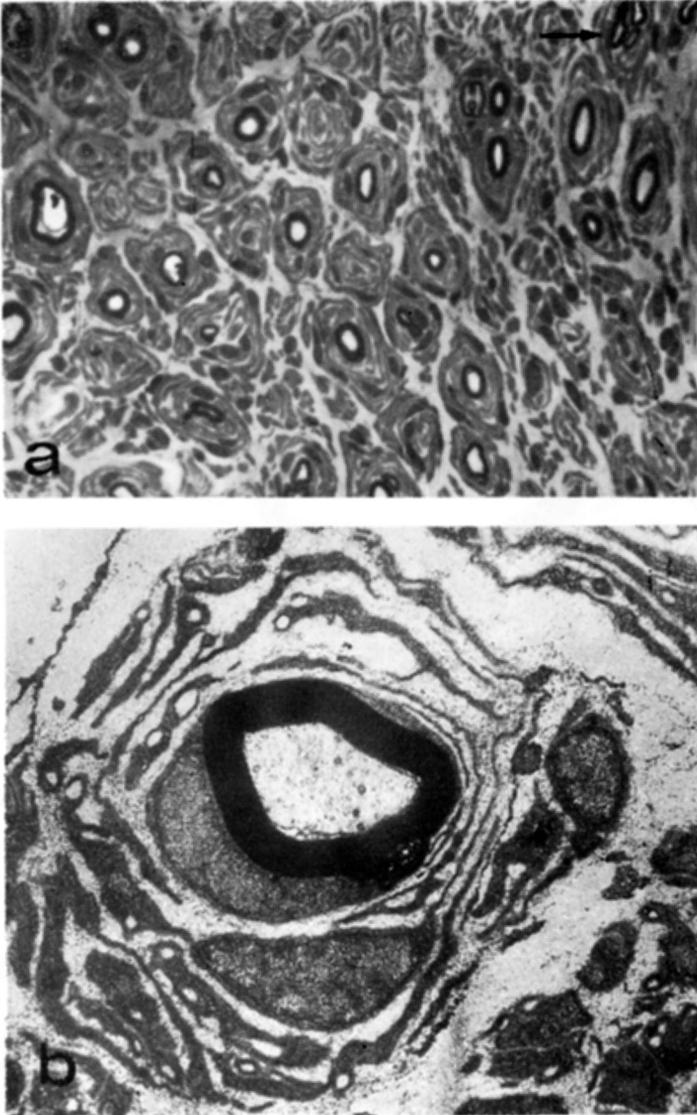


Fig. 4 — a. One micron Araldite section of the nerve from case 3 showing that almost all the fibres are surrounded by Schwann cell cytoplasm concentrically proliferated, with the appearance of onion bulbs; a small cluster of regenerating fibres is seen at upper right (arrow) (Toluidine blue $\times 400$). b. Electronmicrograph of the nerve from case 3 shows one of the numerous onion bulbs seen in this case ($\times 3000$).

COMMENTS

Currently, the diagnosis of chronic recurrent GB syndrome is based on the following criteria^{5,21}: sensory-motor polyneuropathy with slow evolution; progressive or recurrent course; severe reduction of nerve conduction velocity; increased protein level in the CSF; absence of any systemic disease or exposure to toxic substances; and finding of segmental demyelination of peripheral nerves. Although Prineas and McLeod²¹ and Dalakas and Engel⁵ described the illness at all ages from 3 to 60 years, the patients reported by Dyck et al.⁹ were in their 5th and 6th decade of life. On the other hand there is agreement on the absence of sex predominance. The possibility that a genetic predisposition plays a role in the disease is supported by the findings of Aaams et al.¹ who observed that their 14 patients belonged to the HLA types A1, B8, DWE and DRW3, and those of Stewart et al.²³ who found a high incidence of the type HLA DRW3.

The main clinical feature is a mixed polyneuropathy, sometimes with predominance of weakness in proximal muscles. This pattern was seen in our case 2, while in the remaining two cases the distal muscles were the most severely involved. Cranial nerve involvement is not as common as in the acute form^{5,9,21}, and was seen only in our case 1 who presented unilateral 7th nerve palsy. Postural tremor of the upper limbs has been described in some patients by Prineas and McLeod²¹ and Dalakas and Engel⁵; in our case 2 there was hyperkinesia which disappeared after treatment with steroids. The tremor is attributed to involvement of proprioceptive pathways^{5,21}. Bilateral extensor plantar reflex, present in our patient 3, had been previously observed by Prineas and McLeod²¹ in one of their cases.

According to Dyck and Arnason⁸ the evolution of the syndrome can follow 3 courses: steadily progressive or relapsing; the progressive course may stabilize and the patient may eventually recover; a relapsing course in which the attacks may be separated by periods of normality. The recurrence can be spontaneous or may follow the reduction or the withdrawal of the steroid therapy¹⁵⁻¹⁷. Regarding the number of recurrences, the patient described by Natras in 1921¹⁸ presented only two episodes, while that described by Austin³ in 1958 had 20 such episodes over a period of 5 years. The patient reported by Pollard and Selby¹⁹ had two recurrences, both of which followed an injection of tetanus toxoid. Our patients 1 and 2 suffered multiple episodes (7 in 23 years and 5 in 17 years, respectively), which followed the withdrawal of steroids. On the other hand, the progressive course shown in our three patients was also present in the cases described by Bonduelle and Gruner⁴, Torvik and Lundar²⁴, and by Freitas and Nascimento¹².

In addition to the presence of inflammatory cells, oedema and segmental demyelination and remyelination, other features described in chronic GB syndrome include thickening of peripheral nerves and, at histological and ultrastructural level, hypertrophic neuropathy⁸. The latter abnormality was present in two of our three cases. Hypertrophic neuropathy, first described by Natras¹⁸, is however present in a minority of cases^{9,21}. The return of nerves to normal size in the cases described by Austin³ was probably due to improvement of the oedema which was present, in addition to changes of hypertrophic neuropathy. These onion bulbs have been interpreted by many authors as the result of repeated episodes of demyelination²⁵. Axonal degeneration has also been reported in cases of chronic and acute GB syndrome^{9,11}. Feasby et al.¹¹ described 5 patients with a variant of acute GB polyneuropathy who had severe axonal degeneration in distal nerves without inflammation or demyelination. Although we did not find fibres undergoing axonal degeneration we could observe indirect signs of this change such as Schwann cells devoid of axons and small clusters of myelinated axons indicating regeneration. The differential diagnosis of hypertrophic forms with slow evolution have to be made with hereditary diseases like Dejerine-Sottas and Charcot-Marie-Tooth diseases⁷. However, in these two forms there is a family history, dysmorphic changes and they do not improve with the use of steroids.

The use of steroids made the course of chronic GB syndrome more favourable^{3,5,6,9,10,16,17,21}. Remission can be spontaneous or with the use of this drug. Prineas and McLeod²¹ observed among their patients spontaneous remission in 12 occasions and 35 followed steroid therapy. Three out of the 4 patients studied by Hinman and Magee¹³, had spontaneous recovery and one recovered after the use of steroids. Dyck et al.¹⁰ separated their 28 patients in two groups: 14 with and 14 without prednisone and the improvement was much more conspicuous in the group

which used the drug. Our three patients had steroids. All improved and two of them became steroid dependent. It has recently been suggested plasmapheresis as an effective method in the treatment of this disease^{14,22}. However, some more studies are necessary with more patients to evaluate the real efficiency of this therapeutic scheme.

Acknowledgements — We should like to thank: Miss Rita C. Cunha and Miss Suely M. Cunha for the technical assistance, and Miss Rosely C. Cunha and Mr. Ricardo Barreto for the photographic work.

REFERENCES

1. Adams D, Festenstein H, Gibson JD, Hughes RAC, Jarawemada J, Papasteriadis C, Sachs J, Thomas PK — HLA antigens in chronic relapsing idiopathic inflammatory polyneuropathy. *J Neurol Neurosurg Psychiat* 42:184, 1979.
2. Arnason BGW — Acute inflammatory demyelinating polyradiculoneuropathies. In Dyck PJ, Thomas PK, Lambert EW, Bunge R (eds): *Peripheral Neuropathy*. Ed 2. Saunders, Philadelphia, 1984, vol 2, pg 2050.
3. Austin JH — Recurrent polyneuropathies and their corticosteroid treatment. *Brain* 81:157, 1958.
4. Bonduelle M, Gruner J — Polyradiculoneurite progressive. *Rev Neurol* 99:307, 1958.
5. Dalakas MC, Engel WK — Chronic relapsing (dysimmune) polyneuropathy: pathogenesis and treatment. *Ann Neurol* 9 (suppl):134, 1981.
6. DeVivo DC, Engel WK — Remarkable recovery of a steroid-responsive recurrent polyneuropathy. *J Neurol Neurosurg Psychiat* 33:62, 1970.
7. Dyck PJ — Inherited neuronal degeneration and atrophy affecting peripheral motor, sensory, and autonomic neurons. In Dyck PJ, Thomas PK, Lambert EW, Bunge R (eds): *Peripheral Neuropathy*. Ed 2. Saunders, Philadelphia, 1984, vol 2, pg 1600.
8. Dyck PJ, Arnason B — Chronic inflammatory demyelinating polyradiculoneuropathy. In Dyck PJ, Thomas PK, Lambert EW, Bunge R (eds): *Peripheral Neuropathy*. Ed 2. Saunders, Philadelphia, 1984, vol 2, pg 2101.
9. Dyck PJ, Lais AC, Otha M, Bastron JA, Okazaki H, Groover RV — Chronic inflammatory polyradiculoneuropathy. *Mayo Clin Proc* 50:621, 1975.
10. Dyck PJ, O'Brien PC, Oviatt KF, Dinapoli RP, Daube JP, Bartleson JD, Mokri B, Swift T, Low PA, Windebank AJ — Prednisone improves chronic inflammatory demyelinating polyradiculoneuropathy more than no treatment. *Ann Neurol* 11:136, 1982.
11. Feasby TE, Gilbert JJ, Brown WF, Bolton CF, Hahn AF, Koopman WF, Zochodne DW — An acute axonal form of Guillain-Barré polyneuropathy. *Brain* 109:1115, 1986.
12. Freitas MRG, Nascimento OJM — Síndrome de Guillain-Barré de evolução prolongada. *Neurobiologia (Recife)* 34:41, 1975.
13. Hinman RC, Magee KR — Guillain-Barré syndrome with slow progressive onset and persistent elevation of spinal fluid protein. *Ann Int Med* 67:1007, 1967.
14. Levy RL, Newkirk R, Ochoa J — Treating chronic relapsing Guillain-Barré syndrome by plasma exchange. *Lancet* 2:259, 1979.
15. Marchiori PE, Callegaro D, Scaff M, Zambon AA, Assis JL — Polirradiculoneurite recidivante: relato de dois casos. *Arq Neuro-Psiquiat (São Paulo)* 41:208, 1983.
16. Matthews WB, Howell DA, Hughes RAC — Relapsing corticosteroid-dependent polyneuritis. *J Neurol Neurosurg Psychiat* 33:330, 1970.
17. Mello AR, Mattos JP, Cavalcanti JLS — Polirradiculoneurites de evolução prolongada: a propósito de dois casos corticóide dependentes. *Arq Neuro-Psiquiat (São Paulo)* 30:335, 1972.
18. Nattras FJ — Recurrent hypertrophic neuritis. *J Neurol Psychopath (Bristol)* 11:159, 1921.
19. Pollard JD, Selby G — Relapsing neuropathy due to tetanus toxoid. *J Neurol Sci* 37:113, 1978.
20. Prineas JW — Pathology of the Guillain-Barré syndrome. *Ann Neurol* 9 (suppl):6, 1981.
21. Prineas JW, McLeod JG — Chronic relapsing polyneuritis. *J Neurol Sci* 27:427, 1976.
22. Server AC, Lefkowitz J, Braine H, McKhann GM — Treatment of chronic relapsing inflammatory polyradiculoneuropathy by plasma exchange. *Ann Neurol* 6:258, 1979.
23. Stewart GJ, Pollard JD, McLeod JG, Wolmer CM — HLA antigens in the Landry-Guillain-Barré syndrome and chronic relapsing polyneuritis. *Ann Neurol* 4:285, 1978.
24. Torvik A, Lundar T — A case of chronic demyelinating polyneuropathy resembling the Guillain-Barré syndrome. *J Neurol Sci* 32:45, 1977.
25. Webster H DeF, Schroder JM, Asbury AK, Adams RD — The role of Schwann cells in the formation of onion bulbs found in chronic neuropathies. *J Neuropathol* 26:276, 1967.