Acta Pediatr Mex 2004;25(3):168-74

Original article

Pathology of noninflammatory acute flaccid paralysis in Mexico: similarities and contrasts with recent cases studied in China

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RESUMEN

Hace 30 años Ramos-Alvarez y cols. describieron los cambios neuropatológicos en niños mexicanos con parálisis fláccida que fallecieron en la ciudad de México. Estudiamos nuevamente los tejidos impregnados en parafina de 17 de esos casos para compararlos con preparaciones de material de autopsia de 14 casos clínicos similares del norte de China. Cinco de los casos mexicanos y cuatro de los chinos mostraron cambios característicos inflamatorios-desmielinizantes que se han descrito desde hace mucho en la forma clásica de GBS. Los demás casos (12 mexicanos y diez chinos) mostraron fundamentalmente degeneración de los cilindroejes de distribución sólo motora o motora-sensorial. No hubo cambios inflamatorios o fueron mínimos. La mayor parte de los cambios de las células de los cuernos anteriores fueron de naturaleza cromatolítica, pero siete casos (cinco mexicanos y dos chinos, de los cuales uno era inflamatorio) sólo mostraron núcleos contraídos en las células de los cuernos anteriores. Haciendo un balance, los cambios neuropatológicos en el material chino y el mexicano fueron paralelos y llamativamente similares.
Palabras clave: Parálisis fláccida, cambios neuropatológicos, cambios inflamatorios-desmielinizantes, núcleos de los cuernos anteriores, cromatolíticos.

ABSTRACT

Thirty years ago, Ramos-Alvarez and colleagues described the neuropathological changes in children dying with acute flaccid paralysis in Mexico City, with emphasis on 25 non-polio cases. We restudied the paraffin-embedded tissues from 17 of those cases to compare them with paraffin-embedded autopsy material from 14 recent similar clinical cases from northern China. Five Mexican and four Chinese cases exhibited characteristic inflammatory-demyelinating changes long associated with that classical form of Guillain-Barré syndrome. The remainder (12 Mexican and 10 Chinese) showed predominant axonal degeneration, either motor only or motor-sensory in distribution. Minimal to no inflammatory changes were present. A majority of the anterior horn cell changes were chromatolytic in nature, but seven cases (five Mexican and two Chinese, of which one was inflammatory) exhibited only shrunken anterior horn cell nuclei. On balance, the neuropathological changes in the Chinese and the Mexican material were parallel and strinkingly similar.
Key words: Flaccid paralysis, neuropathological changes, inflammatory-demyelinating changes, anterior horn cell nuclei, chromatolytic.

In 1969, Ramos-Alvarez, Bessudo and Sabin described the neuropathological findings in 25 fatal childhood non-polio cases of acute flaccid paralysis (AFP) in Mexico City [1]. Ten had the clinical and pathological characteristics of typical acute inflammatory demyelinating polyneuropathy (AIDP) with mild or none chromatolytic changes in the anterior horn cells [2], the predominant form of the Guillain-Barré syndrome (GBS) in the United States, Europe, Canada and Australia, both then and now. The other 15 cases were distinguished pathologically from AIDP because of the absence of inflammation and demyelination, and because of prominent changes in the anterior horn cells. Those motor neuron changes were divided into two patterns, a "cytoplasmic" pattern characterized by

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Received: March, 2004. Accepted: April, 2004

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severe chromatolysis and a "nuclear" pattern in which the neurons lacked chromatolysis but the nuclei appeared densely stained, irregular in outline, and surrounded by a Nissl-free halo [1].

Recently, forms of the Guillain-Barré syndrome that are denominated by axonal degeneration with only minimal evidence of inflammation or demyelination have been described. The most extensive studies of the pathology of these axonal forms has been conducted on cases from northern China [3]. These cases were divided into a predominantly motor pattern, acute motor axonal neuropathy (AMAN), and acute motor-sensory axonal neuropathy (AMSAN), in which sensory fibers are also affected [3-6]. The AMAN cases are characterized by acute flaccid paralysis, by no sensory involvement, and frequently by albumino-cytological dissociation in the cerebrospinal fluid, with no concurrent fever of other systemic symptoms. Electrophysiologic studies in AMAN are marked by progressive reduction in compound motor action potentials with preserved conduction velocities and sensory nerve action potentials [5,7]. Pathologically, in the acute phases of the illness AMAN is characterized by motor fiber degeneration of widely variable severity and by little or no demyelination, inflammation, or dorsal root involvement [3,4].

The AMSAN cases have similar spinal fluid changes, but the clinical, electrodiagnostic and neuropathologic findings include dorsal root and sensory nerve involvement [8-10].

The close relationship between these axonal patterns is suggested by cases that appear to represent a transition between AMAN and AMSAN, with much more severe ventral than dorsal root involvement [10]. Both AMAN and AMSAN are closely associated with antecedent *Campylobacter* infection [7].

Observation of the Chinese cases dominated by axonal degeneration renewed interest in the Mexican report [1] and raised questions about the similarities or differences of the Chinese cases with the Mexican cases. This study was undertaken to compare the earlier Mexican cases to the recent autopsy series of non-polio acute flaccid paralysis cases for northern China [3].

Original paraffin blocks from the Mexico City series of Ramos-Alvarez and colleagues were recut and studied by immunocytochemical techniques in Baltimore, and paraffin blocks of the Chinese cases were stained in Mexico City, using the same silver and Nissl techniques applied to the original Mexican cases. A greater variety of pathological approaches has been possible with the post-mortem tissue from northern China [3-6,11], including teased nerve fiber studies, electron microscopy, and immunopathological studies. For the purposes of this comparative study, we limited the scope to those standard histological techniques and immunocytochemical techniques that could be carried out with paraffin-embedded material.

METHODS

A total of 31 cases fulfilling the clinical criteria for the diagnosis of GBS were studied, 17 from Mexico and 14 from the Second Teaching Hospital of the Hebei Medical College in Shijiazhuan, People's Republic of China. Archival paraffin-embedded tissue from most of the Mexican cases was extensive, usually including several levels of spinal cord with ventral and dorsal spinal roots, and peripheral nerves. Spinal cord blocks from 11 of the Chinese cases were sent to Mexico City and sections were stained by the same techniques used in the original Mexican series. The stains included hematoxylin and eosin, Bodian silver alone and combined with luxol fast blue and Nissl [1]. The same stains were used on the peripheral nerves and spinal roots in Mexico City. In Baltimore similar sections were stained with hematoxylin and eosin and with a combined Namenko-Feigin silver, luxol fast blue, and periodic acid schiff (PAS) stain. In both sets of tissue it was possible to make an estimate of the extent of demyelination and of Wallerian-like degeneration in the spinal roots and nerves. In the Chinese tissue, it was possible in addition to confirm the cellular pathology identified on the paraffine sections by means of teased fiber preparations, plastic sections and electron microscopy.

From re-embedded and recut paraffine blocks prepared from the 17 cases from Mexico City, as well as the Chinese cases, 6-micron paraffine sections were immunostained for the extent of lymphocytic and macrophage infiltration. For immunocytochemistry [12] sections were rinsed in phosphate-buffered saline (PBS) at pH 7.4, treated with hydrogen peroxide to block

tissue endogenous peroxidase, with non-fat milk and serum to block non-specific protein binding, and with Triton-X to permeabilize membranes. Sections were incubated overnight with specific primary antibodies in nonfat milk and serum. Subsequently, the sections were rinsed in PBS, incubated sequentially with appropriate biotinylated secondary antibody, avidin biotin horseradish peroxidase complex (Vector), and

Table 1. Clinical and Pathological Features of Mexican and Chinese Fatal Cases of acute Flaccid Paralysis

							Pathological changes. Roots-nerves				*Pathological involvement*
Source	*Case*	*Year*	*Age*	*Sex*	*Duration (days)*	*Clinical Symptoms*	*Anterior horn Cells*	*Axons Myeline*	*Lymphocytic Infiltration*	*Macrophage Infiltration*	*PNS*
Mexico	33	65	3	**M**	**1**	**Motor**	**Nuclear**	Axonal	**Mild**	Severe	**Motor/sensory**
	136	66	3	F	1	Motor	Nuclear	Axonal	Mild	Moderate	Motor
	126	66	2	M	3	Motor	Nuclear	Axonal	Rare	Moderate	Motor > sensory
	48	66	3	M	16	Motor	**Nuclear**	Axonal	Mild	Moderate	Motor > sensory
	245	68	4	F	5	Motor	**Nuclear**	Axonal	Mild	Moderate	Motor > sensory
	100	65	10	M	3	Motor	Severe–Chrom.	① Axonal	Mild	Moderate	Motor > sensory
	77	63	5	M	6	Motor/facial	Severe–Chrom.	Axonal	Rare	**Moderate**	Motor
	178	64	5	**M**	6	**Motor**	**Severe–Chrom.**	Axonal	**Rare**	**Moderate**	Motor > sensory
	5	65	7	**F**	6	Motor	Severe–Chrom.	Axonal	Rare	Moderate	Motor
	65	67	7	M	7	Motor	Severe–Chrom.	Axonal	Rare	Rare	Motor > sensory
	15	65	5	**F**	7	Motor	Severe–Chrom.	Axonal	Mild	Mild	Motor > sensory
	6	68	13	M	10	Motor/sensory	Severe–Chrom.	Axonal	Mild	Moderate	Motor > sensory
	49	68	2	F	4	Motor/sensory	Mild – Chrom.	Demyelination	Mild	Moderate	Motor > sensory
	159	67	3	M	5	Motor	Mild – Chrom.	Demyelination	Mild	Moderate	Motor > sensory
	229	68	3	**M**	**12**	**Motor**	**None**	**Demyelination**	**Mild**	**Severe**	**Motor > sensory**
	152	67	3	M	28	Motor	Mild – Chrom.	Demyelination	Moderate	Moderate	Motor > sensory
	149	66	1	M	30	Motor	Mild – Chrom.	Demyelination	Moderate	Moderate	Motor > sensory
China	11	93	1.5	F	5	Motor	None *	Axonal	Rare	Moderate	Motor
	2	91	14	M	7	Motor	Moderate-Chrom.	Axonal	Rare	Rare	Motor
	8	92	56	M	12	Motor	Severe–Chrom.	Axonal	Rare	Severe	Motor
	10	93	22	**M**	4	**Motor**	**Severe–Chrom.**	Axonal	**Rare**	**Mild/Moderate**	**Motor/minimal**
	3	91	28	**F**	8	Motor	None	Axonal	Rare	Rare	Motor/minimal
	1	91	9	F	9	Motor	None	Axonal	Rare	Minimal	Motor/minimal
	13	94	50	M	12	Motor	Severe–Chrom.	Axonal	Rare	Mild	Motor/minimal
	4	91	41	M	7	Motor/sensory	Nuclear	Axonal	Mild	**Mild**	Motor/sensory
	6	91	60	F	18	Motor/sensory	Severe-Chrom.	Axonal	Mild	Moderate	Motor/sensory
	9	92	1.2	**F**	60	Motor/sensory	None **	Axonal	Rare	Moderate	Motor/sensory
	7	92	7	**F**	3	Motor/sensory	**Nuclear**	Demyelination	**Moderate**	**Moderate**	Motor/sensory
	5	91	6	**F**	8	**Motor/sensory**	**None**	**Demyelination**	**Moderate**	Severe	Motor/sensory
	12	93	6	**F**	9	Motor/sensory	None	Demyelination	Moderate	Severe	Motor/sensory
	15	95	-	-	49	-	Moderate-Chrom.	Demyelination	Mild	Mild/Severe	-

*Limited material **Supernormal Nissl bodies ① Chromatolysis
Possible nuclear

filtered 2,3-diaminobenzedine (DAR) (Polysciense) with hydrogen peroxide. The immunocytochemical stains included monoclonal antibody techniques for lymphocyties (CD45) and for macrophages (HAM56).

Overview

The Mexican cases did not differ from the Chinese cases significantly in duration of symptoms prior to death (Table 1). The median age of Chinese cases was 14 years compared to 3 years in the Mexican series. The pathological classification of the cases is presented in table 1. AIDP was judged to be the dominant process in five of the 17 cases from Mexico, in accordance with the original report, and in four of 14 cases from northern China. Axonal degeneration without inflammation or detectable demyelination dominated in 12 of the Mexican cases and ten of the Chinese cases.

Pathological findings in the nondemyelinating cases

Changes in roots and nerves. Extensive ongoing axonal degeneration of the ventral roots with sparing of the dorsal roots was present in three of the Mexican cases (Figure 1A) and three of Chinese cases. Four of the Chinese cases had minimal axonal changes that could be detected only by teased fibers and by electron microcopy [3,4]. The remainder (three Chinese and nine Mexican) of the cases demonstrated varying degrees of axonal degeneration in sensory fibers (dorsal roots), in addition to motor axonal involvement. In cases surviving more than 10 days, secondary tract degeneration in the dorsal columns was apparent. None of these cases had lymphocytic infiltrates in the roots, nerves, or in the spinal cord, but all had macrophage infiltrates (Figure 1B). The macrophage infiltrates in the spinal roots and nerves were restricted to the regions of ongoing axonal degeneration, whether motor or sensory.

In both the Mexican and the seven more severely affected Chinese cases, the hallmark feature was extensive degeneration of motor fibers beyond the roots exit zone. In most cases, the intraparenchymal motor fibers were normal, but occasionally appeared swollen (Figure 1C). Within the limits of paraffin histology, demyelination was absent or minimal in both the Chinese and Mexican material. In the combined silver stains, intact axons without myeline sheaths were not seen, although in regions in which fixation was inadequate the artifactual changes in the myeline sheath often precluded detailed assessment.

Generally, the stage of axonal degeneration in the ventral roots was more advanced than that observed more distally in the peripheral nerves. In some cases in which death occurred within two or three days from onset of neurological symptoms, early degeneration was visible only in the roots (Figure 1D). One case had a different distribution of fiber degeneration, in which the ventral roots were relatively spared with only occasional degenerating fibers, but there was

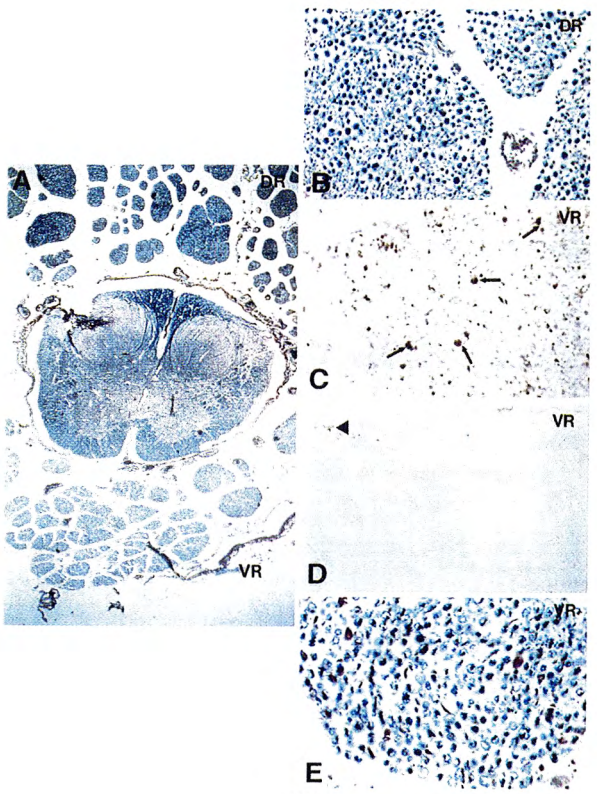

FIG. 1

Figure 1. Lumbar spinal cord from a Mexican patient with non-inflammatory acute flaccid paralysis. The motor nerve cell changes in this case corresponded to those previously described by Ramos-Alvarez et al as cytoplasmic neuronopathy. Note that the dorsal roots (DR) have normal staining in this luxol fast blue -silver stain, but the ventral roots (VR) show marked loss of nerve fibers. At a higher power, the dorsal root (B) confirms the normal appearance of myelinated nerve fibers. In the ventral root there are, by immunostaining for CD68, numerous macrophages. However, immunostains for lymphocytes (LU3) in panel D show only in rare cells within blood vessels. In panel E, at higher power there is loss and ongoing swelling and degeneration of the silver positive axons, reflecting ongoing Wallerian-like degeneration.

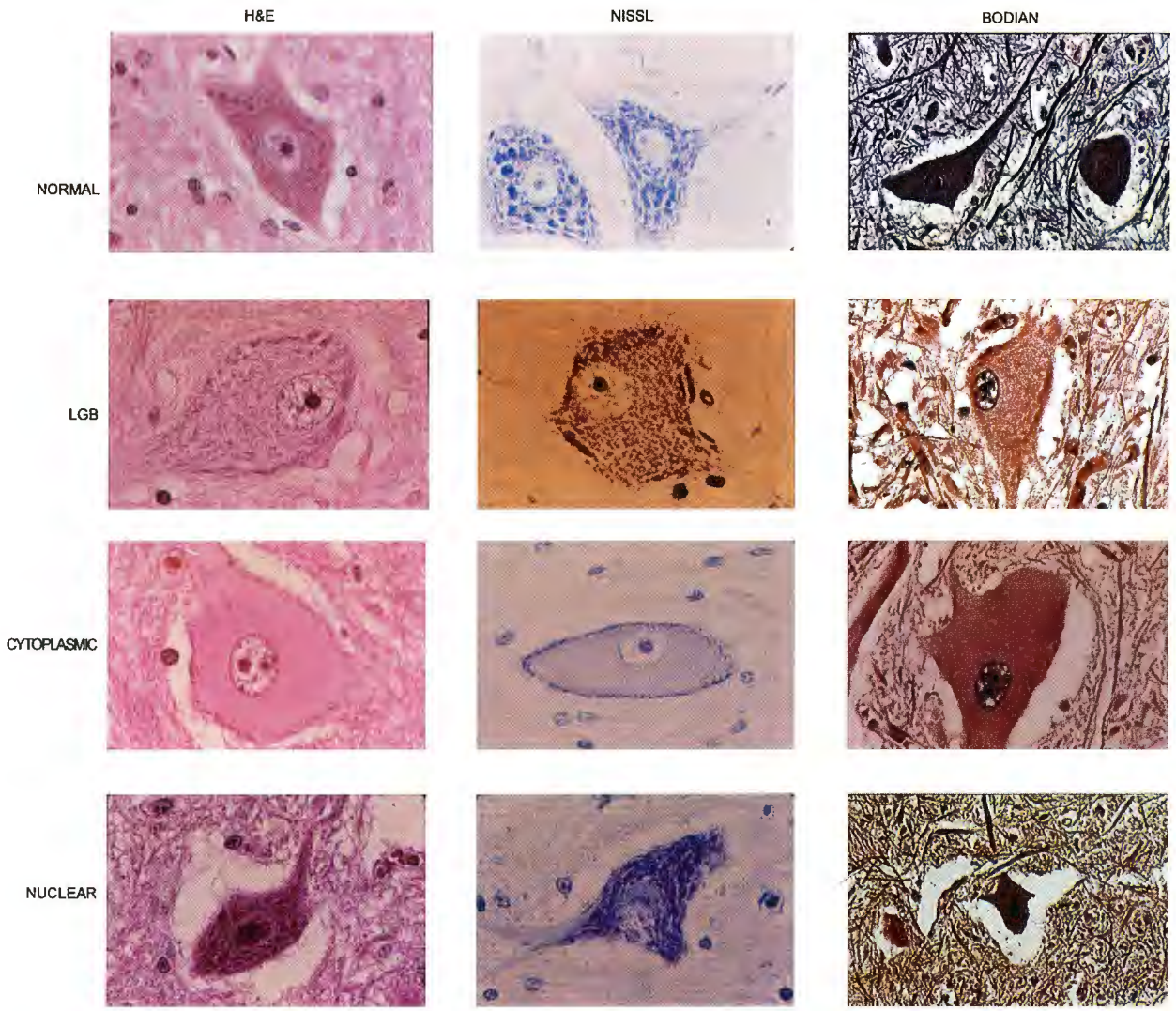

Figure 2. Motor neurons from fatal cases of paralytic diseases and from a case without paralysis in Mexico, stained with hematoxylin and eosin, Nissl and Bodian activated silver. In the category designated Landry-Guillain-Barré (L.GB). There are mild chromatolytic features. In the category designated cytoplasmic neuronopathy the anterior horn cells disclose a severe chromatolysis with a centrally located normal-looking nucleus and a large perikarya. In the category designated nuclear neuronopathy the cells show a dark nucleus with an irregular nuclear membrane and no chromatolysis.

prominent axonal degeneration in the sciatic nerve (Chinese case 8).

Changes in motor neurons

Prominent changes were noted in the anterior horn cells of both the Mexican and the Chinese cases with predominant axonal degeneration. Although the amount of spinal cord tissue available for study in the Chinese cases was not as extensive as in the Mexican material, the nature and extent of anterior horn cell changes were comparable. In the cases showing chromatolytic change ("cytoplasmic neuronopathy") in the original Mexican publication [1], both Chinese (five cases) and Mexican (seven cases), perikareya were swollen to twice the expected size, Nissl bodies were dispersed, but nuclei almost always remained centrally placed.

Five Mexican cases and one Chinese axonal case exhibited contracted, irregular, densely staining nuclei

with a surrounding clear halo (nuclear neuronopathy). This change was most readily recognized with the Bodian stain, although it was also evident on hematoxylin and eosin stain. None of these nuclear cases had chromatolytic changes in other anterior horn cells.

Patterns of cellular reaction

As noted, lymphocytic infiltration was rare in the axonal patterns. The presence of occasional lymphocytes within the lumen of endoneural vessels indicated that the immunocytochemical reactions were technically satisfactory. Perivascular cuffs were not seen, and only rare lymphocytes were present within the endoneural space. The numbers of endoneural lymphocytes were scanty in both early and late nondemyelinating cases compared to the demyelinating cases.

In contrast, there was intense immunostaining for macrophages in both Mexican and Chinese material with active nerve fiber degeneration (Figure 1C.) macrophages were evident even in cases dying two or three days after onset of neurological symptoms, but they were much more numerous in later cases. Macrophage infiltrates were similar in cases showing neuronal nuclear changes as well as those showing chromatolytic changes. In combined LFB-HAM 56 stains, some macrophages were seen in cross-section to be encircled tightly by myeline sheaths. By electron microscopy, in the Chinese material, such macrophages were shown to be frequent and were localized within the internodal periaxonal space [3,4,10].

Pathological findings in the inflammatory demyelinating cases

Five of the Mexican cases and three Chinese cases demonstrated demyelination of nerves and roots with readily appreciated lymphocytic infiltration in perivascular and diffuse distributions, and with large numbers of activated macrophages in the endoneural space between nerve fibers (Figure 1E). We considered these cases to be typical of AIDP [2]. As previously noted, the degree of lymphocytic infiltration varied, but lymphocytes were generally present, even in the cases with the longest intervals between onset and death. Chromatolysis was present in many of these cases, but was relatively mild, affected a minority of the anterior horn cells, and exhibited an eccentrically placed neuronal nucleus in many instances. In one Chinese case (case 7), anterior horn cells manifested only contracted, densely staining, irregular nuclei with a clear halo, designated as nuclear neuronopathy.

DISCUSSION

We restudied the autopsy neuropathological material from fatal non-polio cases of acute flaccid paralysis in Mexico City, and compared it to similarly prepared autopsy neuropathological material from fatal cases of clinical Guillain-Barré syndrome (GBS) in northern China. The pathological material from both the Mexican and the Chineses fatal cases separated clearly into two major categories, i.e., cases with inflammatory demyelination and cases with non-inflammatory axonal degeneration. The inflammatory demyelinating cases in both the Mexican and Chinese material were typical acute inflammatory demyelinatin polyneuropathy type of Guillain-Barré syndrome [2]. In the non-inflammatory axonal degeneration cases the peripheral nerves and the anterior horn cell changes were similar in the Mexican and the Chinese material.

Increasingly, it is recognized that GBS includes several related syndromes, all of which fit beneath the umbrella of the diagnostic criteria, but which differ from each other not only in some clinical features, but also by pathological and electrodiagnostic features.

The present results confirm two central aspects of the previous description of the Mexican series by Ramos-Alvarez, Bessudo and Sabin [1]: the absence of lymphocytic infiltration in the spinal cord, peripheral nerves, or roots; and the prominence of anterior horn cell changes. Further, this study extends the original report [1] by characterizing the extensive axonal degeneration in the PNS of the Mexican cases. The combination of silver stains coupled with macrophage markers provide a sensitive means of assessing ongoing Wallerian-like degeneration. Most of the nondemyelinating Mexican cases had extensive axonal degeneration of the ventral roots and motor nerves. Over half also had dorsal root and sensory nerve involvement, although usually not as severe as the ventral root involvement. The degeneration of motor fibers was often visible just outside the spinal cord in

the ventral root exit zone; this was true for the most severe Mexican and Chinese cases. Occasionally, the intraparenchymal motor axons showed axonal swelling.

Four Chinese cases exhibited only minimal pathologic changes by paraffine histology, despite severe paralysis leading to their demise. Extensive studies of the Chinese cases, using high-resolution techniques and reported elsewhere [3,4], revealed a sequence of pathologic and immunopathologic changes not visible in these paraffine sections that led to their classification as mild or early AMAN.

Anterior horn cell changes

Most of the predominantly axonal cases from both Mexico and China had perikaryal enlargement and dispersion of Nissl. These cases, termed "cytoplasmic neuronopathy" by Ramos-Alvarez et al [1], conform in general to the features of severe chromatolysis. Compared to the AIDP cases, the chromatolysis was much more prominent. A former distinction from AIDP, at present unexplained, is that in the axonal cytoplasmic cases the nucleus was centrally located in the cell body, whereas in the AIDP cases with chromatolysis the nucleus was often eccentric, the usual finding in chromatolysis. In any event, we think it likely that the changes in the axonal cases occurred in response to a primary injury to the axon. Ramos-Alvarez et al [1] suggested that the perikaryal changes might reflect primary injury to the nerve cell body. We cannot exclude the possibility that in the axonal cases these perikaryal changes can reflect an immune–mediated attack on the motor neuron soma as well as the axon. If so, it seems likely to be antibody-mediated, given the lack of inflammation in the ventral horn.

The second group of cases, termed "nuclear neuronopathy" by Ramos-Alvarez et al [1], was distinguished by irregular intensively argyrophilic nuclei in vast majority of neurons with little or no chromatolytic response. Such anterior horn changes were seen in two of the Chinese series, one with AIDP and one with only axonal abnormalities. The significance of this nuclear change is unknown.

In brief, this comparative study using well-established paraffin histological approaches to study recent autopsy material from China and Mexican material from clinically similar cases from 30 years ago shows striking similarities pathologically and relatively modest differences. We tentatively conclude that most, if not all, Chinese cases of acute flaccid paralysis without inflammatory demyelination and classified as AMAN or AMSAN in 1995 are the same as the Mexican cases classified by Ramos-Alvarez et al [1] as "cytoplasmic or nuclear neuronopathies" in 1968.

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