Fragmentation of the Golgi Apparatus of Motor Neurons in Amyotrophic Lateral Sclerosis

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*The Golgi apparatus (complex) is at the center stage
of important functions of processing and transport
of plasma membrane, lysosomal, and secreted pro-
teins. The involvement of the Golgi apparatus in the
pathogenesis of chronic degenerative diseases of neu-
rons is virtually unknown. In the present study, frag-
mentation and atrophy of the Golgi apparatus of
motor neurons in amyotrophic lateral sclerosis
(ALS), has been detected with organelle specific an-
tibodies. Approximately 30% of motor neurons in
five ALS patients showed a fragmented Golgi appa-
ratus whereas only about 1% of motor neurons from
seven controls with neurologic or systemic disease
showed a similar change. Morphometric studies are
consistent with the hypothesis that the alteration of
the Golgi apparatus is an early event in the patho-
genesis of the neuronal degeneration in ALS. Immu-
nocytochemical studies with antibodies against al-
pha tubulin, tau, and phosphorylated subunits of
neurofilament polypeptides did not disclose differ-
ences in the staining of neurons with fragmented or
normal Golgi apparatus, suggesting that the alter-
ation of the organelle is not secondary to a gross
lesion of the cytoskeleton. However, these observa-
tions do not rule out the hypothesis that the fragmen-
tation of the Golgi apparatus is secondary to subtle
changes of the polypeptides involved in the attach-
ment of membranes of the organelle to the cytoskel-
eton. (Am J Pathol 1991, 140:731–737)*

Amyotrophic lateral sclerosis (ALS) is a chronic, incur-
able disease characterized by degeneration of motor
neurons and atrophy of skeletal muscle. Sensory and
high cortical functions are spared. The etiology of the
degeneration of motor neurons in ALS is unknown. Hy-
potheses have included a lack of target-derived growth
factors, endogenous or exogenous toxins, viral infec-
tions, immune dysfunction, endocrine abnormalities,
trauma, impaired DNA repair, abnormal axonal transport,
and genetic factors.[1,2]

Insights into the pathogenesis of the degeneration of
motor neurons may be derived from the application of
cellular or molecular probes to ALS tissues. A recent
study with an organelle-specific antiserum against MG-
160, a 160 kDa sialoglycoprotein of medial cisternae of
the Golgi apparatus (GA), showed fragmentation of the
organelle in three patients with ALS.[3] It was suggested
that the observed fragmentation of the GA of motor neu-
rons was similar to that induced by depolymerization of
microtubules.[4,5]

This study confirmed the initial observation of frag-
mented GA of motor neurons in tissues from a new group
of ALS patients probed with two additional organelle-
specific antibodies, to include in the control group pa-
tients with other neurologic or systemic disease, and to
examine the hypothesis that alterations in the neuronal
cytoskeleton are associated with the fragmented GA.

Materials and Methods

Tissues from five patients with ALS and seven controls
with other neurologic or systemic disease were studied
with one antiserum and two monoclonal antibodies
against intrinsic membrane polypeptides of the GA (Ta-
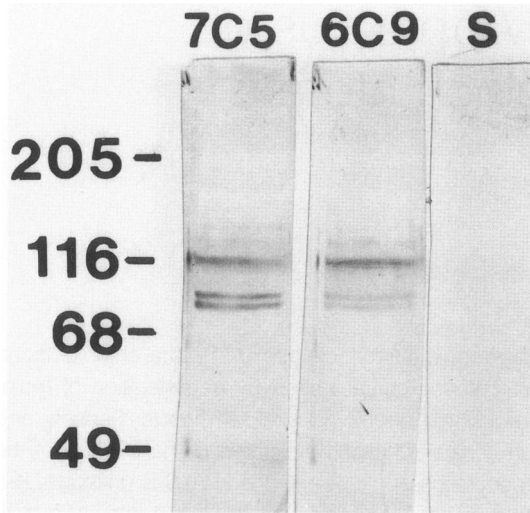bles 1, 2; Figure 1). The diagnosis of ALS, established

Figure 1. *Organelle-specific monoclonal antibodies 7C5 and 6C9 were screened by Western blotting after electrophoresis in 7.5% polyacrylamide gels in the presence of β-mercaptoethanol; 60 μg of protein of a crude membrane fraction from human brain, prepared according to previously described methods[8] were electrophoresed; SP, Supernatant of SP2 cells (control); 7C5 and 6C9 reveal polypeptides of 110 kDa and a doublet of 90 kDa apparent molecular mass.*

from clinical and laboratory studies, was confirmed at autopsy by the typical findings of loss of motor neurons in the spinal cord and medulla, axonal spheroids (dystrophic axons), mild gliosis in affected areas, atrophy of anterior roots and neurogenic atrophy of skeletal muscle. In addition, Bunina bodies and skein-like inclusions were seen in a small number of motor neurons.[6] Loss of myelinated axons in the corticospinal tracts, of varying intensity, was observed. None of the patients with ALS had the familial form of the disease.

A polyclonal, organelle specific, antiserum raised against immunoaffinity purified MG-160, a sialoglycoprotein of medial cisternae of rat neuronal Golgi apparatus and monoclonal antibodies GC9 and 7C5 raised against enriched fractions of the Golgi apparatus from cultured human melanoma cell line A-875, obtained from the American Culture Collection, were used.[7,8] Monoclonal antibodies to enriched Golgi fractions were raised according to previously detailed methods.[8] The specificity of these antibodies to the Golgi apparatus was established by light and immunoelectron microscopy, and the apparent molecular mass of the antigen(s) was studied

by Western blotting as previously described.[8] Tissues obtained at autopsy were fixed for 6–8 hours at room temperature in 1% freshly made paraformaldehyde in buffered physiologic saline and washed and embedded in paraffin as previously described.[7] In a previous study, we reported in detail the immunocytochemical procedure and the various fixatives used in an attempt to optimize the detection of the Golgi apparatus. Apparently the antigen, MG-160, is sensitive to strong fixatives and prolonged fixation.[7] Five-micron-thick sections, incubated with 1:1,500 dilutions of the rabbit antiserum against MG-160, were incubated with goat-antirabbit IgG coupled to biotin and were stained with the avidin-biotin modification of the indirect immunoperoxidase method.[7] Sections incubated with preimmune serum were negative. Morphometric studies were done with a CUE-2 image analyzer using the planomorphometry program (Olympus, Lake Success, NY).

Results

The novel organelle specific antibodies 7C5 and 6C9 were screened by Western blotting and light and ultrastructural immunocytochemistry with cultured melanoma cells and human brain tissue obtained at autopsy. Both monoclonal antibodies reacted with polypeptides of 110 kDa and with a doublet of 90 kDa in apparent molecular mass of crude membrane fractions obtained from human brain obtained at autopsy (Figure 1). By immunoelectron microscopy done with human melanoma cells, monoclonal antibody 6C9 stained predominantly Trans cisternae of the Golgi apparatus, whereas monoclonal antibody 7C5 stained predominantly medial cisternae of the organelle (Figures 2, 3). The identical staining pattern of Western blots obtained with the two monoclonal antibodies and the slight differences of the ultrastructural immunocytochemical results suggest that the two monoclonal antibodies recognize either the same or closely related polypeptides. Both monoclonal antibodies and the polyclonal serum against the Golgi apparatus gave identical results in the stains of the human spinal cords; however, for consistency, in the morphometric studies only the antiserum was used.

Sections of cervical, thoracic, and lumbar cord from

Table 1. *Patients with Amyotrophic Lateral Sclerosis*

No. case	Origin	Age	Sex	Duration	Death/autopsy (hr)
90–244	HUP	80	M	3 years	5
90–14	CBH	67	F	2.5 years	6
90–181	HS	47	M	5 years	2
90–45	BCM	70	F	2.3 years	2
90–13	B	73	M	9 months	13

Table 2. *Controls*

No. case	Age	Sex	Cause of death	Death/autopsy (hr)
90–246	61	F	Idiopathic cardiomyopathy Extensive ischemia of the gastrointestinal tract	5
90–145	64	M	Myasthenia gravis	12
90–135	53	F	Down's syndrome	15
90–26	31	F	Right cerebral hemispheric infarction	9
90–83	65	M	Diffuse Lewy body dementia Gaucher's disease	11
90–93	69	M	Alzheimer's disease	19
90–161	78	M	Carcinoma of lung	5

all five patients with ALS, stained separately with one polyclonal and two monoclonal antibodies recognizing intrinsic membrane polypeptides of the GA, showed fragmentation of the organelle in numerous motor neurons (Figure 4). An identical staining pattern of the GA was obtained with the three organelle specific antibodies that were used. Frequently, motor neurons with a fragmented GA were adjacent to motor neurons with a normal appearing GA (Figure 4). The fragmentation of the GA was noted in the large motor neurons in the anterior horns of the spinal cord, whereas neurons of the nucleus dorsalis (column of Clarke), which usually is not affected in ALS, had a normal GA.

To examine the specificity of the fragmentation of the GA observed in ALS cases, the organelle was studied by immunocytochemistry and morphometry in seven controls affected by other neurologic or systemic diseases (Table 2). Fragmented GA was observed in motor neurons from control cases, but in significantly lower numbers than in ALS (Table 3). Thirty percent of motor neurons in ALS had fragmented GA in contrast to only 1% of
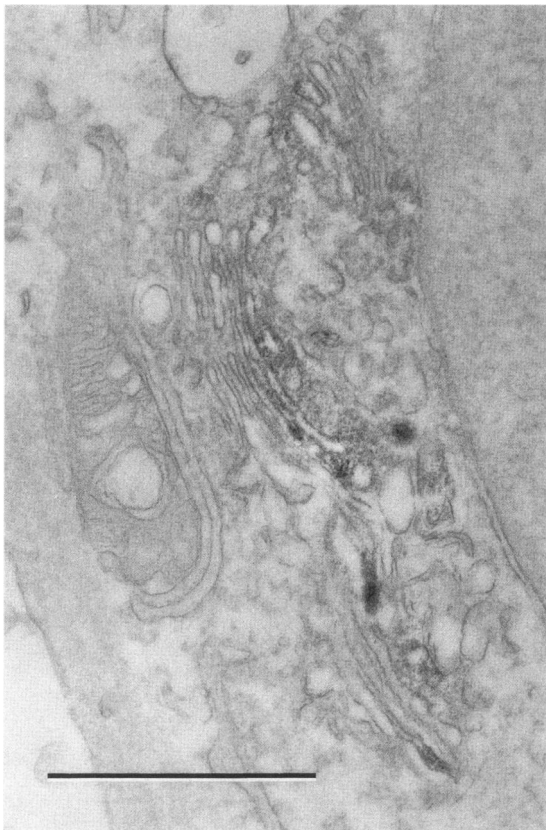

Figure 2. *Ultrastructural immunocytochemistry of cultured human melanoma cells stained with monoclonal antibody 6C9 according to a previously detailed method.[8] Immunoperoxidase reaction product is deposited in cisternae of the concave (Trans) aspect of the Golgi apparatus. Adjacent nucleus, nuclear and plasma membranes, mitochondrion and cisternae of the rough endoplasmic reticulum are not stained, magnification 36,000, bar = 1 μm.*
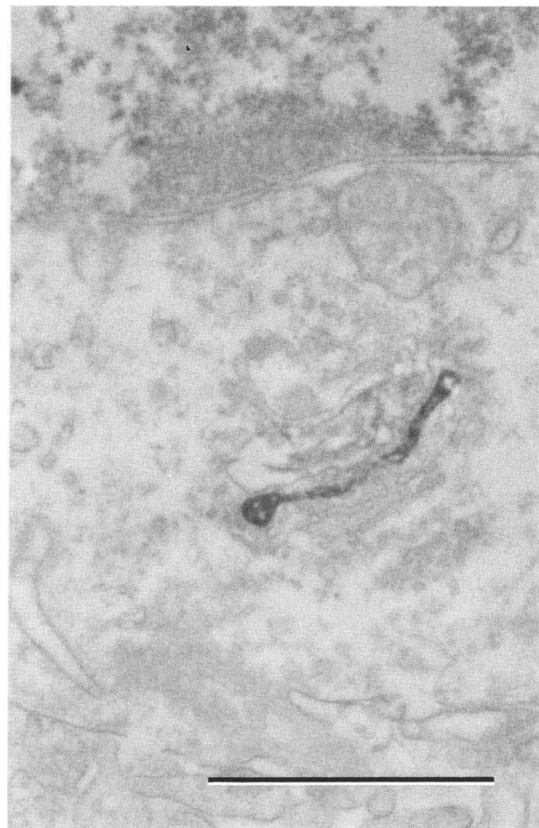

Figure 3. *Same as in Figure 2 except that monoclonal antibody 7c5 was used. Note staining of medial cisternae of the Golgi apparatus, magnification 38,000, bar = 1 μm.*
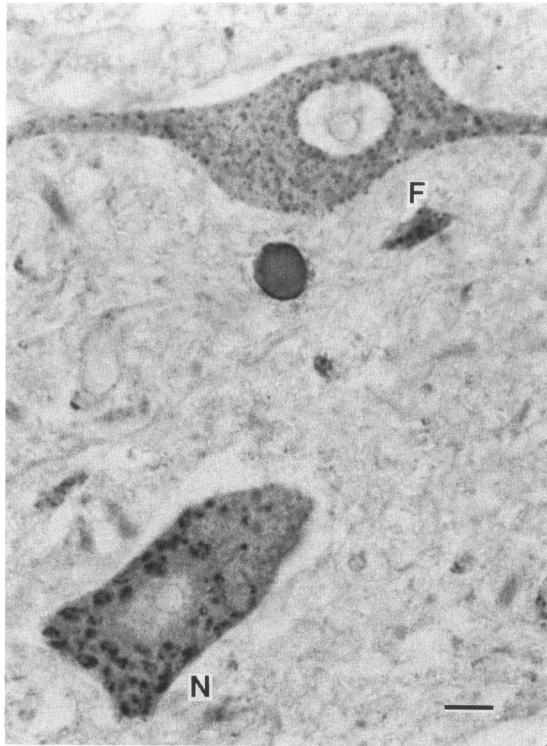
Figure 4. *Light microscopic immunocytochemistry of a section of cervical spinal cord from a patient with ALS. Paraffin sections, 5-micron thick, were immunostained according to described methods, using an antiserum against MG-160, a sialoglycoprotein of membranes of medial Golgi cisternae, the avidin-biotin peroxidase method, and Diaminobenzidine tetrahydrochloride as substrate.[7] F, motor neuron with fragmented GA; N, motor neuron with normal GA, magnification 700, bar = 10 μm.*

motor neurons from controls (Table 3). When the percentages of motor neurons with fragmented GA of individual cases with ALS were examined, significant differences among these numbers were detected. Thus, 8–53% of motor neurons from ALS had fragmented GA in compar-

Table 3. *Quantitation of Motor Neurons with "Fragmented" Golgi Apparatus*

	No. neurons	% Frag.
ALS (5)	1261	29.6
Controls (7)	1872	1

Five-micron thick serial sections of low cervical (C6-8), midthoracic and lumbar spinal cord from patients with ALS and controls were numbered and stained with an antiserum specific for the human GA. To avoid counting a motor neuron twice, only every 12th section was used in the quantitative study. The identification of the slides was covered with a tape, the slides were mixed, examined blindly by two (N.K.G., A.S.), and the scores averaged. Neurons with discrete, small and granular immunostained GA were scored as fragmented (Frag.). Neurons with larger and irregular profiles of immunostained GA, often in the form of rings displaying a central unstained area, were scored as normal. In addition, a category of motor neurons with a pattern of immunostained GA, which was transitional between the normal and fragmented organelle, was identified. Because of the small percentage of neurons with the "transitional" form of the GA, and a considerable variance of the score between the two examiners, this category of neurons is not included in these tables.

Table 4. *"Fragmentation" of the Golgi Apparatus of Spinal Cord Motor Neurons per ALS Case*

No. case	Origin	% Frag.	No. of neurons examined
90–244	HUP	21.4	439
90–14	CBH	52.6	128
90–181	HS	8.3	108
90–45	BCM	43.7	58
90–13	B	17.8	528

See legend to Table 3.

ison to 0–3% of motor neurons from controls (Tables 4, 5). Interestingly, the ALS case with the smallest number of fragmented GA had the longest clinical course of 5 years (Tables 1, 4). The wide range of percentages of motor neurons with fragmented GA in ALS may correlate with the speed of the progression of the neuronal degeneration. The two control cases with the highest percentages of motor neurons with fragmented GA suffered from myasthenia gravis and Alzheimer's disease (Tables 2, 4).

Morphometric studies in ALS and control cases showed that in motor neurons with fragmented GA, the number of Golgi elements increased, whereas the mean surface area of individual GA and the total area occupied by the GA per cell decreased in comparison to corresponding results obtained in motor neurons with an apparently normal morphology. In contrast, the cell area of motor neurons with fragmented GA was not significantly smaller than the area of normal neurons in ALS (Table 6). However, comparisons of mean cell areas, mean sizes of individual GA and total areas occupied by the GA per cell between normal motor neurons in ALS and controls showed that in ALS the mean cell area, the mean size of individual immunostained elements of the GA, and the surface area occupied by the GA was significantly lower in the ALS normal motor neurons than in controls (Table 7). Morphometric studies of surface areas of nuclei did not disclose any significant differences between ALS motor neurons with a normal or fragmented GA or controls.

Taken together, the morphometric studies in ALS are consistent with the conclusions that the fragmentation of the GA occurs in motor neurons with a moderately de-

Table 5. *"Fragmentation" of the Golgi Apparatus of Spinal Cord Motor Neurons per Control Case*

No. case	% Frag.	No. of neurons examined
90–246	0	349
90–145	2.6	230
90–135	0	248
90–26	0.3	253
90–83	0	172
90–93	2.8	319
90–161	0.9	211

See legend to Table 3.

Table 6. *Morphometric Studies in Motor Neurons in ALS with Fragmented and Apparently Normal Golgi Apparatus*

	Mean cell area/μ^2	Golgi elements/cell	Mean golgi/size/μ^2	% Golgi/cell
Fragmented	702.3 ± 27.2	53.1 ± 3.8	.314 ± 0.018	2.78 ± 0.28
Normal	640.1 ± 32.6	29.8 ± 1.86	1.200 ± 0.082	5.30 ± 0.05
P	NS	< 0.005	< 0.005	< 0.005

P values are based on Student's t test; NS = not significant, P value greater than .05; 90 cells from each category were analyzed. Five-micron thick sections of motor neurons, including nuclei were analyzed; measurements of the perimeter and surface area of nuclei did not show statistically significant differences among the three groups of neurons analyzed, namely from controls, ALS neurons with fragmented GA, and ALS neurons with normal GA. Because of the small numbers of control motor neurons with a fragmented GA, this group was not analyzed. To avoid analyzing a cell twice, of the serial sections only every 12th section was included in the study; 130 neurons from controls were examined; the numbers per case varied from 15 to 35; in ALS, 75 neurons with normal GA were analyzed and the per case numbers varied from 15 to 28; also in ALS, 90 motor neurons with fragmented GA were analyzed and the per case numbers varied from 15 to 30.

creased cell area, and that the morphologically normal GA in motor neurons in ALS shows a reduced size as compared with controls (Table 7). Therefore, it is tempting to speculate that the fragmentation of the GA is preceded by an atrophy of the organelle.

The dependence of the structural integrity of the GA on cytoskeletal elements, principally microtubules, has been suggested by numerous studies.[4,5] To further explore any possible correlations between fragmented GA and changes of immunoreactivities to cytoskeletal antigens, we examined, in 5 micron consecutive thick serial sections of spinal cord, whether the immunostain for the normal or fragmented Golgi apparatus correlated with markers for alpha tubulin, tau, and phosphorylated neurofilaments. Antibodies against tau (T-6402) were purchased from Sigma (St. Louis, MO), and against alpha tubulin (N-356) from Amersham, Arlington Heights. The antibody against the phosphorylated NFH and NFM neurofilament subunits (TA51) was supplied by Dr. W. Schlaepfer.[9]

Immunocytochemical studies with the aforementioned antibodies with sections of spinal cord from ALS and control patients did not reveal any differences in the intensity and patterns of staining between motor neurons with fragmented or intact appearing GA, arguing against a role of the cytoskeleton in the pathogenesis of the fragmentation of the organelle. As described previously by Schmidt and collaborators, dystrophic axons in ALS stained with the antibody against the phosphorylated epitopes of the two neurofilament subunits.[10] In Figures 5 and 6, we show in consecutive serial sections an identical stain for phosphorylated neurofilaments in neurons with fragmented or normal Golgi apparatus. Similar results

were obtained with antibodies against alpha tubulin and Tau.

Discussion

The central role of the GA in the processing and targeting of membrane and secretory polypeptides has been investigated extensively.[11] The GA is also involved in the endocytosis of exogenous ligands, and most likely, in the recycling of cell surface receptors in various cell types.[11-14] There is ample evidence on the role of the GA in experimental pathologic reactions, but factual information in human disease is limited.[15]

The fragmentation of the GA in motor neurons in ALS may have functional implications in view of its importance in numerous processes. Although the immunocytochemical evidence presented here does not support the hypothesis that the described changes of the GA are secondary to cytoskeletal lesions, this hypothesis has not been ruled out considering the paucity of information on the molecular basis of the linkage between the GA and the cytoskeleton and the limitations of the immunocytochemical method used in tissue sections to detect subtle differences in the intracellular patterns of cytoskeletal elements.[11]

A small number of motor neurons from control cases showed fragmented GA (Tables 3–5). This result suggests that the GA of motor neurons, and possibly of other types of cells, displays considerable plasticity and that the fragmentation of the GA may represent a stage of a potentially reversible series of alterations of the structure and function of the organelle. In the case of ALS, frag-

Table 7. *Morphometric Studies in Motor Neurons with Apparently Normal Appearing Golgi Apparatus in ALS, and in Controls*

	Mean cell area/μ^2	Golgi elements/cell	Mean golgi size/μ^2	% Golgi/cell
ALS	640.1 ± 32.5	29.8 ± 1.86	1.200 ± 0.082	5.30 ± 0.34
Controls	738.3 ± 33.3	27.9 ± 1.41	1.950 ± 0.090	6.99 ± 0.25
P	<0.025	NS	< 0.005	< 0.005

P values are based on Student's t test; NS = not significant, P value greater than .05; 90 cells from ALS and 130 from controls were analyzed. See legend to Table 6.
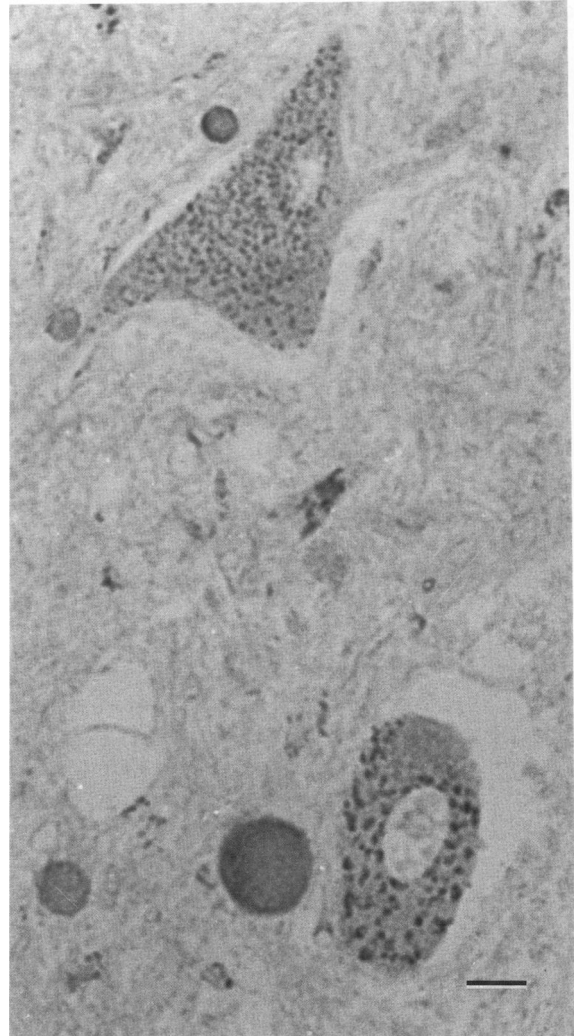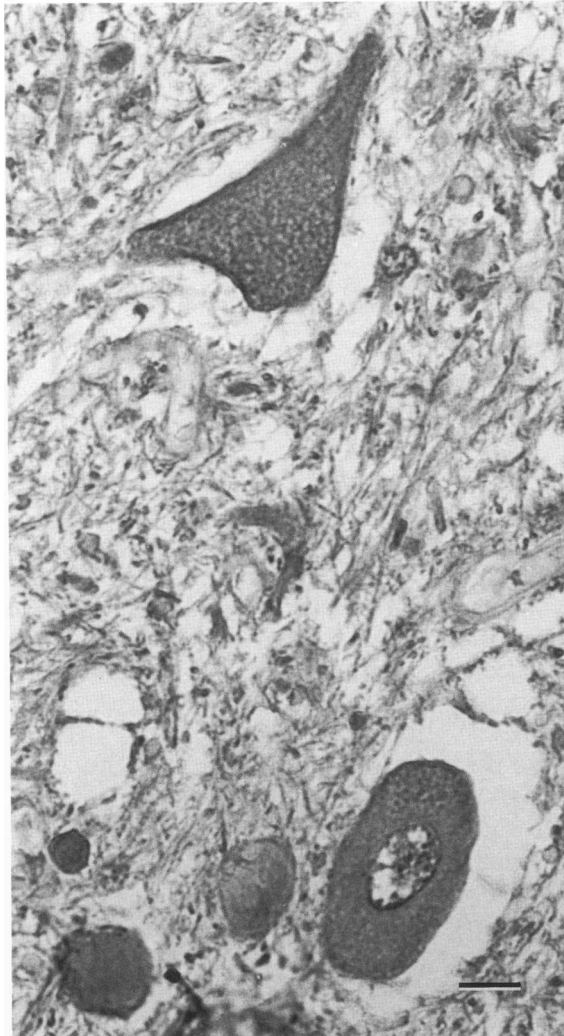
Figure 5. *Spinal cord section, 5 micron thick, from a patient with ALS stained with an antibody against phosphorylated subunits of neurofilaments. Both neurons show a similar stain in the perikarya. Round bodies at the lower part of the figure are "spheroids" or dystrophic axons, magnification 800, bar = 10 μm.*

Figure 6. *Consecutive, 5 micron thick, section from the same block as in previous figure, stained with a polyclonal antiserum against MG-160, a marker of the Golgi apparatus. Note that the neuron at the upper part of the figure shows a fragmented Golgi apparatus in contrast to the neuron at the lower part of the figure which shows the usual staining of the organelle; magnification × 800, bar = 10 μm.*

mentation of the GA of motor neurons may precede loss of function and the eventual degeneration of individual motor neurons.

The observed alteration of the GA in ALS is consistent with certain etiologic hypotheses.[2] The shrinkage of ALS motor neurons and the fragmentation of the GA may result from the withdrawal of target derived neurotrophic factors.[2,16] The observed alteration of the GA in ALS may subsequently impair fast components of the axoplasmic flow and deprive axon terminals of important constituents. Alternatively, an endogenous or exogenous toxin may cause fragmentation of the GA by affecting linkages of the organelle with the cytoskeleton.[17–19] Aberrant autoimmune responses to cell surface antigens, such as ion channels, may initiate a cascade of reactions leading to

the fragmentation of the GA, cell atrophy, and death.[20–23] Finally, the changes of the GA may be caused by impaired repair or expression of genes that are crucial for the biogenesis and stability of the GA, or the various cytoskeletal elements to which the organelle is attached. The aging neuron may be particularly susceptible to these changes.

In ALS, dispersion and/or peripheral displacement of the Nissl granules, i.e., chromatolysis, has been observed.[6] The fragmentation of the GA may be linked to the chromatolytic reaction. In experimental chromatolysis, a reduction of the surface area occupied by individual Golgi elements occurs, as well as a reduction of the percentage of the cytoplasmic area occupied by the GA.[24]

Regardless of the initiating event, fragmentation of the GA may be an early, and possibly reversible, step in the subsequent degeneration of motor neurons in ALS.

References

1. Tandan R, Bradley WG: Amyotrophic lateral sclerosis. Part 2: Etiopathogenesis. Ann Neurol 1985, 18:419–431
2. Appel SH: A unifying hypothesis for the cause of amytrophic lateral sclerosis, Parkinsonism and Alzheimer disease. Ann Neurol 1981, 10:499–505
3. Mourelatos Z, Adler H, Hirano A, Donnenfeld H, Gonatas JO, Gonatas NK: Fragmentation of the Golgi apparatus of motor neurons in amyotrophic lateral sclerosis revealed by organelle-specific antibodies. Proc Natl Acad Sci USA 1990, 87:4393–4395
4. Robbins E, Gonatas NK: Histochemical and ultrastructural studies on HeLa cell cultures exposed to spindle inhibitors with special reference to the interphase cell. J Histochem Cytochem 1964, 12:704–711
5. Turner JR, Tartakoff AM: The response of the Golgi complex to microtubule alterations: The roles of metabolic energy and membrane traffic in Golgi complex organization. J Cell Biol 1990, 109:2081–2088
6. Hirano A: Aspects of the ultrastructure of amyotrophic lateral sclerosis. Human Motor Neuron Diseases. Edited by L. P. Rowland. New York, Raven Press, 1982, pp 75–88
7. Croul SE, Mezitis SGE, Stieber A, Chen Y, Gonatas JO, Goud B, Gonatas NK: Immunocytochemical visualization of the Golgi apparatus in several species, including human, and tissues with an antiserum against MG-160, a sialoglycoprotein of rat Golgi apparatus. J Histochem Cytochem 1990, 38:957–963
8. Gonatas JO, Mezitis SGE, Stieber A, Fleischer B, Gonatas NK: MG-160: A novel sialoglycoprotein of the medial cisternae of the Golgi apparatus. J Biol Chem 1989, 264:646–653
9. Lee VM-Y, Carden MJ, Schlaepfer WW, Trojanowski JQ: Monoclonal antibodies distinguish several differentially phosphorylated states of the two largest neurofilament subunits (NF-H and NF-M) and demonstrate their existence in the normal nervous system of adult rats. J Neurosci 1987, 7:3474–3488
10. Schmidt ML, Carden MJ, Lee VM-Y, Trojanowski JQ: Phosphate dependent and independent neurofilament epitopes in the axonal swellings of patients with motor neuron disease and controls. Lab Invest 1987, 56:282–294

11. Farquhar MG: Progress in unraveling pathways of Golgi traffic. Annu Rev Cell Biol 1985, 1:447–488
12. Gonatas NK, Kim SU, Stieber A, Avrameas S: Internalization of lectins in neuronal GERL. J Cell Biol 1977, 73:1–13
13. Gonatas J, Stieber A, Olsnes S, Gonatas NK: Pathways involved in fluid phase and adsorptive endocytosis in neuroblastoma. J Cell Biol 1980, 87:579–588
14. Gonatas NK: The role of the neuronal Golgi apparatus in centripetal membrane vesicular traffic. J Neuropathol Exp Neurol 1982, 41:6–17
15. Morre DM: Role of the Golgi apparatus in cellular pathology. J Electron Microsc Tech 1991, 17:200–211
16. Barde YA: Trophic factors and neuronal survival. Neuron 1989, 2:1525–1534
17. Rothstein JC, Tsai G, Kuncl RW, Clawson L, Cornblath DR, Drachman DB, Pestronk A, Sauch BL, Coyle JT: Abnormal excitatory aminoacid metabolism in Amyotrophic Lateral Sclerosis. Ann Neurol 1990, 28:18–25
18. Perry TL, Kreiger C, Hansen S, Eisen A: Amyotrophic Lateral Sclerosis: Aminoacid levels in plasma and cerebrospinal fluid. Ann Neurol 1990, 28:12–17
19. Plaitakis A: Glutamate dysfunction and selective motor neuron degeneration in amyotrophic lateral sclerosis: A hypothesis. Ann Neurol 1990, 28:3–8
20. Engelhardt J, Appel SH: IgG reactivity in the spinal cord and motor cortex in amyotrophic lateral sclerosis. Arch Neurol 1990, 47:1210–1216
21. Appel SH, Engelhardt J, Garcia J, Stefani E: Immunoglobulins from animal models of motor neuron disease for human amyotrophic lateral sclerosis patients passively transfer physiological abnormalities to the neuromuscular junction. Proc Natl Acad Sci USA 1991, 88:647–651
22. Delbono O, Garcia J, Appel SH, Stefani E: IgG from amyotrophic lateral sclerosis affects tubular calcium channels of skeletal muscle. Am J Physiol 1991, 260:C1347–C1351
23. Hays AP, Roxas A, Sadiq SA, Vallejos H, D'Agati VD, Thomas FP, Torres R, Sherman WH, Bailey D, Braxton AG, Hays AG, Rowland LP, Latov N: A monoclonal IgA in a patient with amyotrophic lateral sclerosis reacts with neurofilaments and surface antigens in neuroblastoma cells. J Neuropathol Exp Neurol 1990, 49:383–398
24. Croul SE, Mezitis SGE, Gonatas NK: An anti-organelle antibody in pathology. The chromatolytic reaction studied with a monoclonal antibody against the Golgi apparatus. Am J Pathol 1988, 133:355–362